# Heading Mindfully from Automatization to Deliberation: Cue-reactivity and Cognitive Control

Dissertation

Zur Erlangung des Grades eines Doktors der Naturwissenschaften

der Mathematisch-Naturwissenschaftlichen Fakultät und der Medizinischen Fakultät

der Eberhard-Karls-Universität Tübingen

vorgelegt von

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März – 2018

**Tag der mündlichen Prüfung:** 31.7.2018

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***Danksagung***

Zunächst möchte ich Prof. Fallgatter, Prof. Hautzinger und Prof. Nürk danken, für den wertvollen wissenschaftlichen Input im Rahmen des Advisory Boards der „Graduate Training Center of Neuroscience“, der ich an dieser Stelle ebenfalls danken möchte. Ich danke Prof. Fallgatter für die Unterstützung und die Ressourcen zur Umsetzung der geplanten Forschungsvorhaben. Prof. Hautzinger möchte ich neben dem wissenschaftlichen Input auch für den therapeutischen Input im Rahmen der Psychotherapie-Ausbildung danken. Danke für die Unterstützung der Kombination dieser beiden Perspektiven, die ich persönlich als besonders bereichernd empfinde. Ann-Christine Ehlis gilt mein Dank aus mindestens zwei Gründen: 1. Für die ausgesprochene fachliche Kompetenz als Mentorin und die beste Arbeitsgruppenleitung die ich mir vorstellen kann. Und 2. Als Freundin, für die Bereicherung der Promotionszeit mit vielen schönen Momenten und einem stets offenen Ohr.

Von ganzem Herzen möchte ich auch meinen Eltern, Jacek, Betty, Jan und Annika für den Ausgleich und die verständnisvolle Unterstützung und Geduld danken. Auch Frank möchte ich danken für die Unterstützung im Endspurt und für die Entspannungsmomente!

Und auch den anderen, die meinen Alltag mit Freude und Leben erfüllt und meine Promotionszeit unvergesslich gemacht haben, möchte ich danken: Saskia, danke für die vielen einsichtsreichen Gespräche und auch die Momente die gar nicht so sinnvoll waren, aber spaßig. Auch den weiteren Mitgliedern der Arbeitsgruppe „Psychophysiologie und optische Bildgebung“ möchte ich danken für die Bereicherung im Laboralltag! Danke Helena, Thomas, BS für die gemeinsame Zeit im Sonnenzimmer und der damit einhergehenden Maximierung der Freude am Arbeitsplatz und produktiven gemeinsamen Projekte. Danke Helikopter, für Zuckerbrot und Peitsche. Danke Thomas, fürs Teilen deines großen Wissenschatzes. Danke BS, für die Vermittlerrolle bei Matlab. Danke Dusty, als mein mehrmaliger Retter in der Not was Programmierung betrifft. Liebe Ramona, liebe Betti, danke für die praktische Unterstützung und Kriseninterventionen im Laboralltag.

Danke auch an das Team der Station 22 für das, was ich dort über das DBT lernen durfte und die achtsame Haltung, welche ich dadurch einnehmen konnte… Nicht nur als Therapeutin sondern auch im Rahmen dieser Dissertation konnte ich davon davon profitieren.

*„Wer noch nie einen Fehler gemacht hat,*

*hat sich noch nie an etwas Neuem versucht”*

- *Albert Einstein*

***Abbreviations***

| | |
|---|---|
| AUDIT | Alcohol Use Disorder Identification Test |
| ACC | Anterior Cinguclate Cortex |
| BOLD | Blood-Oxygen-Level-Dependent |
| CET | Cue-Exposure Therapy |
| dlPFC | dorsolateral Prefrontal Cortex |
| EEG | Electroencephalography |
| EHI | Edingburgh Handedness Inventory |
| ERN | Error-Related Negativity |
| ERP | Event-Related Potentials |
| fMRI | functional Magnetic Resonance Imaging |
| fNIRS | functional Near-Infrared Spectroscopy |
| FTND | Fagerström Test for Nicotine Dependence |
| HD | Heavy social Drinkers |
| HHb | deoxygenated Haemoglobin |
| HRV | Heart-Rate Variability |
| IDTSA | Inventory of Drug Taking Situations - Alcohol |
| LD | Light social Drinkers |
| LPP | Late Positive Potential |
| LTD | Long-Term Depression |
| LTP | Long-Term Potentiation |
| Ne | error-Negativity |
| OFC | Orbitofrontal Cortex |
| PANAS | Positive and Negative Affect Schedule |
| PES | Post-Error Slowing |
| ROI | Region-Of-Interest |
| SUD | Substance Use Disorders |
| tDCS | transcranial Direct Current Stimulation |
| TMS | transcranial Magnetic Stimulation |
| VTA | Ventral Tegmental Area |

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**Summary**

Human behavior is driven by automatic and deliberative processes. In contrast to fast automatic processing, deliberative processes rely on cognitive control. Substance use disorders (SUD) are featured by an imbalance of automatic and deliberative behavioral regulation. Error-monitoring is one aspect of cognitive control affected by SUD. Error-monitoring is the prerequisite for the adaption of automatized behaviors with unfavorable outcomes. Impairments in cognitive control in SUD are accompanied by cue-reactivity, the automatized response to drug-related cues. Both mechanisms are related to the severe impairments in decision making in SUD. Cue-reactivity is established via repeated consumption of a drug and is expressed at an autonomic (sympathetic activity), cognitive (craving) and behavioral (drug-seeking behavior) level. The 1-year abstinence rate for SUD treatment is 40-60%, which depicts the challenging modification of cue-reactivity involved in relapse (McLellan et al., 2000).

The aim of this work was the transfer of the concept of mindfulness on the relation of cue-reactivity and cognitive control. Accordingly, neuroscientific approaches focusing on this context will be discussed. The transfer of experimental research in this field to clinical practice allows developments in SUD treatment. Complementary, observations from clinical practice contribute to a better understanding of natural human brain functioning. This allows the establishment of eligible neuroscientific paradigms in reverse. Both views will be addressed within this work. The discussion is based upon results of four studies:

**Study 1:**

Visual alcohol cue-reactivity was analyzed in heavy social drinkers (HD) and light social drinkers (LD). Cue-reactivity was found in HD at an early attentional processing level (P100 latency) and during the processing of motivational significance (LPP amplitude). P100 latency and LPP amplitude predicted Alcohol Use Disorder Identification Test (AUDIT) scores. These effects were specifically found in relation to the recognition of alcohol content, not in the visual-feature control condition with unrecognized scrambled beverage pictures. Effects were driven by alcoholic-content, not the visual features of the pictures. Therefore, results encouraged the use of individualized stimulus-sets in cue-reactivity paradigms.

**Study 2:**

Cue-reactivity effects on error-monitoring were measured in HD and LD, using simultaneous functional near-infrared spectroscopy (fNIRS) and electroencephalography (EEG). Although error-monitoring (error-related negativity, ERN/ error negativity, Ne) was affected by visual alcoholic cues in HD, there was no impairment at the behavioral level. Conclusively, differences in error-compensation strategies between HD and LD were discussed.

**Study 3:**

Cue-reactivity and cognitive control were assessed during in-vivo smoking cue-exposure in smokers and non-smoking controls. Besides fNIRS measurement of the prefrontal cortex, subjects rated their craving verbally during cue-exposure. Craving was selectively elicited in smokers. Hemodynamic activity in the dorsolateral prefrontal cortex (dlPFC) and the orbitofrontal cortex (OFC) did not differ significantly between groups. Nevertheless, functional connectivity between dlPFC and OFC was significantly increased in smokers.

**Study 4:**

Immediate effects of transcranial direct current stimulation (tDCS) on cue-reactivity and cognitive control during smoking cue-exposure were measured via fNIRS, craving and heart-rate variability (HRV). HRV was added as measure to assess the autonomic level of cue-reactivity. Anodal tDCS over the left dlPFC with the cathode above OFC significantly increased functional connectivity during smoking cue-exposure in smokers. This effect neither affected HRV nor craving ratings.

## 1. Introduction

Everybody errs; therefore, it is useful to adapt previous behavior after errors. This process allows goal-directed behavior, even though errors occur. Although errors are a common feature of human action, they do not always lead to failure, as they can be corrected immediately (Frese & Keith, 2015). Ongoing performance-monitoring – involving the registration of errors – is a prerequisite for behavioral regulation enabling goal-directed behavior. Psychiatric diseases are featured by cognitive errors related to behavioral dysregulation. For this work, neuroscientific literature on behavioral regulation was considered, as well as developments in behavioral therapy, focusing on the modification of human behavioral dysregulation. Understanding the underlying brain mechanisms of behavioral dysregulation in psychiatric diseases reveals approaches for its modification in terms of therapeutic interventions.

Still, the reciprocity of this relation needs to be addressed: Clinical practice is the empirical evidence for modification of dysregulated brain mechanisms. Therefore, neuroscientific study designs can benefit from observations of successful or failed behavioral modification in psychiatric diseases. A holistic view on human behavioral regulation requires not only insights from brain activity, but likewise its relation to behavioral outcomes. Furthermore, a thorough understanding of the behavioral outcomes can help to formulate relevant hypotheses in neuroscientific research. This feedback loop of methodological adaption after their practical application promises further insights on the understanding of human behavioral regulation. Therefore, not only the transfer of neuroscientific results to therapeutic implications, but likewise implications of developments in behavioral therapy for neuroscientific approaches are discussed within this work.

To explain human behavioral regulation, dual-process theories (Evans & Stanovich, 2013) describe the interaction of deliberative and automatized processes. SUD are featured by a severe behavioral dysregulation, characterized by an impairment of deliberative and an amplification of automatized processes (Carpenter et al., 2015). Repeated substance consumption forms cue-reactivity, an automatized response to drug-related cues, via mechanisms of classical and operant conditioning. Evidence from relapse prevention in SUD reveals that its retraining has small to moderate effect sizes (Walter et al., 2015). Therefore, the challenges of SUD treatment will be discussed in the respective section.

Nevertheless, cue-reactivity is not specific for SUD. Regular drug consumers develop cue-reactivity as well, however, they are able to compensate this automatic component via cognitive control. That, in turn, enables healthy subjects to inhibit an automatized response (cue-reactivity)

when it interferes with goal-oriented behavior. Deliberative decision-making reflects the evaluation of interfering goals to achieve the most favorable outcome.

This work focuses on the interplay of automatized (cue-reactivity) and deliberative (cognitive) processes in HD and smokers. The deliberative processing of automatized processes is closely related to the *"mindful perspective"* that will be inferred in the following. Current developments in behavioral therapy are based upon a *"mindful perspective"* as well. Both domains will be considered for an integrated view.

### 1.1 Developments in behavioral therapy

The beginning of behavioral therapy ranged from the early 20$^{th}$ century (Watson, 1913) until the 1950s/1960s. It was based on the principles of classical (Pavlov, 1927) and operant conditioning (Skinner, 1938). The rational described human behavior as driven by its reinforcing value. In other words, a positive outcome increases the occurrence of a behavior, while punishment decreases the occurrence of the precedent behavior. This regulation of overt behavior, according to its reinforcement, is termed operant conditioning (Skinner, 1938). Classical conditioning explains motivational salience of initially neutral stimuli (Pavlov, 1927). This "first wave" of behavioral therapy was driven by scientifically established principles and broke down the complexity of explaining behavior from a psychoanalytical perspective (Hayes et al., 2016). At the same time, this "first wave" of behavioral therapy neglected inner-subject processes in the description of human behavior. If this perspective could explain human behavioral regulation throughout, a change in reinforcing contingencies, e.g. a medication that induces immediate sickness after alcohol consumption, should be sufficient as relapse prevention in patients with alcohol dependency, nevertheless, it is not (Skinner et al., 2014). Focusing SUD treatment, this conclusion from the "first wave" of behavioral therapy is therefore insufficient.

Therefore, this limited perspective was extended by thoughts and feelings, establishing cognitive behavioral therapy, termed the "second wave" of behavioral therapy (Ellis, 1962; Beck et al., 1979). Since then, expectations, assumptions about the environment and the cognitive appraisal of a situation have become important characteristics in the explanation of human behavior. The modulation of a perception induced by the alterations of its appraisal was highlighted. This perspective focused on inner processes, explaining observations not explainable by classical learning theories. Rational-emotive behavioral therapy (Ellis, 1973) was applied to attenuate problematic affects (e.g. anxiety, depression) by the modulation of the accompanied problematic thoughts. The identification of cognitive errors and their correction by reasoning provided a variety of helpful

interventions. Behavioral principles were assimilated into cognitive behavioral therapy (Hayes, 2016, Hautzinger, 1993). In SUD treatment, permission-giving thoughts related to consumption are identified, as well as dysfunctional assumptions about the own person, situations, other people that increase the relapse risk.

However, there are still cases when the alteration of problematic thoughts is insufficient to adapt behavior. The “third wave” encounters such problems with a more contextual approach (Hayes, 2016). “Third wave” interventions aim at the modification of thought function independent of its problematic content, which was the target of “second wave” interventions. Thus, the main target in SUD treatment in “third wave” interventions is no longer to prevent craving, but rather the modification of its handling. The philosophical background for those interventions is the defusion of toxic thoughts (which has been already focused within the “second wave”), acceptance, a focus on individual values and mindfulness (Hayes, 2016). Mindfulness became the fundament of “third wave” interventions. Summarized, mindfulness describes the current perception with a distance to immediate action (Kabat-Zinn, 2003). Therefore, mindfulness has a close relation to the present moment and a deliberation of automatized processes.

Although emotional processing is automatized, it can be transferred into conscious perception (cf. Linehan, 1993). Emotions are evolutionary old, involving bodily sensations, cognition and behavior. They are elicited by environmental cues or internal states. The acceptance of the current state, involving emotions into decision-making, without automatically following its implications, is a mindful path from automatization to deliberation. Modern approaches relying on introspection during exposure (cf. **Study 3**, **Study 4**) can be accounted to the “third wave” (Hayes, 2016) aiming at a conscious perception of automatized processes as well. From a classical behavioral perspective, habituation is the mechanism underlying exposure, leading to a decline of the feeling intensity. Modern approaches, however, highlight the reframing of the self as the observer of a feeling (defusion). Nevertheless, the gain of “third wave” interventions has been doubted. Still, there is a development from mere control of problematic thoughts of feelings to the acceptance of the current state, even when not foreseen or desirable. The goal then is to evaluate own behavior in the modified context according to own values to re-orientate. Not changing the content of thoughts, but rather the emphasis on change of awareness and relationship to thoughts has been argued as development of cognitive behavioral therapy (Hayes, 2016).

Behavioral therapy has always been closely related to empirical evidence from studies with high scientific standards. This highlights the importance of neuroscientific basics for the development of therapeutic interventions. A “*mindful perspective*” on the brain now suggests that the close relation

of science and cognitive behavioral therapy is reciprocal. Therefore, the next section will focus on developments in neuroscience and interrelation to a clinical perspective on human behavioral regulation.

### 1.2 Developments in neuroscience

With the beginning of experimental psychology (Wundt, 1878), psychophysiological reactions to highly standardized, fine-grained external stimuli were applied to analyze differences in human behavioral reactions within the laboratory. Perceptual judgments to external stimuli were analyzed without consideration of inner-subject processes. This perspective is closely related to the aforementioned “first wave” concept of behavioral therapy, as subjects were regarded as a “black box” producing responses to external stimuli.

As technology improved, neuroimaging methods were developed enabling the additional assessment of human brain functioning, describing cognition. EEG (Berger, 1929) allowed measuring electrophysiology related to cognitive processes with high temporal resolution. Other developments in neuroscience allowed improvements in spatial resolution, simplifying localization of functional activity to anatomic structures, e.g. using fMRI (since the 1990s). This method relies on increased blood coverage in activated brain regions inducing changes in blood oxygenation. While the concentration of oxygenated hemoglobin increases, deoxygenated hemoglobin has an opposed time course. Oxygenation measures are limited by a temporal lag of the hemodynamic response (peaks with about 8 s delay). Studies using the imaging approach relate distinct cognitive processes to brain structures. As imaging studies focus on the content of cognitive processes, they are closely related to the idea of the “second wave” of behavioral therapy. The focus on task-specific changes (content) in distinct brain regions assumes straightforward processes in the human brain. Connectivity analyses are an approach to overcome such constrictions of task-related activity to a specific region, involving the activity context (Gonzalez-Castillo & Bandettini, 2017). Content specific region-of-interest analysis can be complemented by a context-related identification of connectivity patterns. The focus on current brain states is a parallel approach to the acknowledgment of context factors, additionally to content, highlighted in “third wave” approaches of behavioral therapy. Some promising neuroscientific approaches and methods involving “third wave” ideas will be introduced in the following.

*1.2.1. Electroencephalography (EEG)*

EEG measures electrophysiological brain responses induced by post-synaptic activity of simultaneously active spatially aligned neurons generating a dipole at the scalp (Luck, 2005). The analysis of distinct cognitive processes is linked to a task or a sensory stimulation with a high temporal resolution. Event-related potentials (ERP) are identified within the averaged responses. They are related to a specific condition (motor responses, external stimuli or inner processes). In **Study 1** and **Study 2**, this ERP approach was applied. The high temporal resolution comes along with a poor spatial resolution. A methodological combination can overcome the shortcomings each method has inherited and provides more information about activity context. In **Study 2**, ERP data was supplemented by information about changes in prefrontal hemodynamics captured by functional near-infrared spectroscopy (fNIRS). FNIRS is a very convenient and easily applicable method that can be used to supplement ERP analysis in simultaneous assessments by adding spatial information; it will therefore be described in the following section.

*1.2.2 Functional near-infrared spectroscopy (fNIRS)*

The scientific application of fNIRS increased within the past 20 years, especially in psychiatry (Ehlis et al., 2014). As in fMRI, the signal is based on increases in blood flow after local brain activation (BOLD response; Jöbsis, 1977). The peak of the event-related BOLD response occurs about 6 seconds after a response/task/sensory perception. Still, a shortcoming of fNIRS is the restriction to outer cortical layers and no possibility to image neuroanatomic structures. Nevertheless, the method is highly relevant with several advantages compared to fMRI (Cutini & Brigadoi, 2014): Exclusion criteria are sparse, application is cheap, acceptance in subjects is increased, as well as ecological validity (allowing small movements and subjects sitting in an upright position). The latter point is addressed in the current work and the "third wave" ideas. **Study 3** supported the applicability of fNIRS to capture dlPFC and even OFC (extending to the outer layer of the outer cortex only to a small extent) activity during small movements. A common approach adapted from fMRI is the analysis of task- or group-related differences in regions-of-interest (ROI analysis). Still, results are often inconclusive. Connectivity analyses provide a better understanding of such inconclusive results by the registration of activity context. Connectivity was analyzed in **Study 3** and **Study 4** additionally to ROI analysis.

In **Study 2** and **Study 4**, another very important advantage of fNIRS was used: the interference-free application with methods based on electrical signals such as EEG and transcranial direct current stimulation (tDCS). Within **Study 4**, an fNIRS measurement was conducted

simultaneously to active tDCS, a very prominent non-invasive brain stimulation technique, which will be described in the following.

### *1.2.3 Transcranial direct current stimulation (tDCS)*

Non-invasive brain-stimulation techniques such as tDCS and transcranial magnetic stimulation (TMS) gained significance in the treatment of psychiatric diseases, due to a low side-effect profile and high acceptance in patients (Kuo et al., 2017). tDCS alters cortical excitability underneath the electrodes by modulating membrane potentials subthresholdly (Nitsche & Paulus, 2000, Nitsche et al., 2003). A weak constant current is delivered from anode to cathode, the two electrodes applied on the scalp surface. Long-term potentiation (LTP) is promoted by anodal tDCS via glutamatergic mechanisms activated by a decrease of the membrane potentials (Nitsche et al., 2003). Cathodal tDCS, however, is related to short-term hyperpolarization and long-term depression (LTD; Nitsche & Paulus, 2003). Both mechanisms contribute to neuroplasticity, by a strengthening (LTP) or a weakening of neuronal pathways (LTD), respectively. Duration, strength and polarity of tDCS stimulation influence the effects on basic brain mechanisms and still require further research (Nietsche et al., 2005).

LTP in the ventral striatum is involved in the evolvement of cue-reactivity (Kauer, 2004). Therefore, it is relevant to investigate the effects of tDCS evoked LTP during cue exposure. Within **Study 4**, tDCS was applied during an fNIRS measurement. Results confirmed that fNIRS is a convenient method to measure online changes in hemodynamic cortical activity during tDCS. Although the NIR light cannot penetrate the black tDCS electrodes, hemodynamic responses adjacent to the electrodes were captured. Measuring immediate effects of the stimulation on hemodynamics can be used to find optimal stimulation parameters for the clinical application of tDCS. Moreover, context effects during non-invasive brain-stimulation techniques need to be considered (Silvanto et al., 2007), which is in line with the “third wave” idea in neuroscientific approaches. An implementation will be introduced in the following.

### *1.2.4 Increasing ecological validity*

Experiments in the laboratory environment provide high internal validity, still there is the need to increase ecological validity additionally, to capture a more realistic perspective on human brain functioning (Ladouce et al., 2017). Stationary NIRS allows small movements and is therefore a convenient method to investigate hemodynamic activity of the brain in realistic situations. Portable devices even allow leaving the laboratory completely. The objective of **Study 3** was to increase the

ecological validity of prefrontal cortical measurements within the laboratory by an in vivo smoking cue-exposure. In **Study 4**, the ecological validity of the paradigm was further increased by using the individually preferred tobacco brand and giving verbal instructions by the examiner instead of audio-records. After eliciting cue-reactivity, the aim was a conscious perception of current cognitive, bodily and emotional states without following the elicited urge to smoke. Acknowledging the current state is a prerequisite for deliberative decision-making in contrast to automatization. This idea reflects the concept of mindfulness, which is basic in "third wave" psychotherapeutic interventions. Adapting this concept for neuroscientific research allows a conscious perception of automatized processes in human brain functioning and therefore provides a promising contribution for its understanding. Using the aforementioned methods, this work focused on new developments in neuroscientific research inspired by clinical experience. Especially interactions of cue-reactivity and cognitive control were investigated from different perspectives. A better understanding of the transition from automatized to deliberative processes promises improvements in the clinical induction of these processes. Hence, in the following, the interplay of these processes in healthy individuals and patients with SUD will be introduced.

## 2. Theoretical Background

### 2.1 Regulation of human behavior: deliberative and automatic processes

Rapid judgments rely on automatic processing and are adaptive in nature, in a world full of external stimulation (Kahnemann & Frederick, 2002; Evans & Stanovich, 2013). Deliberative processing, however, is necessary when a problem occurs or something unexpected happens, like changes in reinforcement contingencies or errors. Those events require additional effort for behavioral adaption (Shenhav et al., 2013). Dual-system models of human behavioral regulation posit that areas of the brain reward system such as the Nucleus Accumbens or the ventro-medial PFC (including the OFC) generate automatic behavioral responses, whereas deliberative processes, relying on executive functioning, involve the dlPFC and posterior parietal cortex (Sanfey & Chang, 2008).

Automatized processing relies on dopaminergic neurons in reward-related brain areas. Hereby, subcortical processes evoke automatic attentional guidance. Those dopaminergic neurons are highly sensitive to reward predicting cues (Schultz et al., 1997) and therefore allow conditioning. Although consciousness is not a prerequisite for conditioning, such automatized processes can be

made in a conscious way. This concept was already introduced as mindfulness, allowing a transition from automatized to deliberative processing.

One example for evoked deliberative decision making in the laboratory is the delay of gratification paradigm (McClure & Bickel, 2014). Delay of gratification is the ability to withstand an immediate reinforcement, in order to gain something more valuable, yet not immediately available. It requires planning, reasoning and the inhibition of a predominant response (Mischel, 1974). Hereby, conflict is induced by the immediate availability of a reinforcement (processed in the OFC) that has to be rejected in order to gain a more valuable reinforcement that is not yet available. The dlPFC down-regulates value-related responses in the OFC which receives input from the midbrain dopaminergic system, processing reinforcements (Hare et al., 2009). Compared to automatic processes, deliberative decision making requires additional effort for planning, attention, working memory, and error- and conflict-monitoring (Fuster & Bressler, 2015). Error-monitoring and conflict-monitoring, are examples of executive functioning, capturing the need for the transition of automatized to deliberative behavioral regulation. Therefore, the focus will be narrowed to both processes involved in performance monitoring in the next section to illustrate the underlying mechanism more precisely.

### *2.1.1 Performance monitoring (Focusing error-monitoring and conflict-monitoring)*

Goal-directed behavior requires constant performance monitoring and behavioral adaption. Performance monitoring refers to the constant comparison of a situation, involving own behavior and the desired outcome. Error-monitoring is necessary when differences between desired and actual outcome occur. In the laboratory, error-monitoring and subsequent behavioral adaption can be investigated reliably in reaction tasks, e.g. the Eriksen Flanker task (cf. **Study 2**). The error-related negativity (ERN; Gehring et al., 1993) / error negativity (Ne; Falkenstein et al., 1991) is a fast (up to 100 ms) medial-frontal negative ERP locked to response errors. Source localization studies identified the anterior cingulate cortex (ACC) as the most likely generator for the ERN/Ne (van Veen & Carter, 2002).

Reinforcement learning theory (Holroyd & Coles, 2002) and the conflict-monitoring theory (van Veen & Carter, 2002) are the most pervasive hypotheses on ERN/Ne functionality. Reinforcement learning theory postulates that errors are signaled via the mesencephalic dopaminergic system, communicating that an effect is worse/better than expected. The basal ganglia induce this signal by an increase/decrease in phasic midbrain dopamine activity. When an event is worse than expected, dopaminergic neurons disinhibit motor neurons within the ACC, which

in turn evokes the ERN/Ne. The mesencephalic dopamine system even allows learning of automatized responses via signals to the basal ganglia and frontal cortex (Holroyd & Coles, 2002). According to the conflict monitoring hypothesis (van Veen & Carter, 2002), however, the ACC is activated by competing response options, signaling the need for the suppression of a distractor. Therefore, the error signal triggers attentional adjustments whenever necessary (Botvinick et al., 2001). Supporting this view, also high response conflict trials elicited an ERN/Ne-like component (Carter et al., 2000). The N2 is another ERP measure for performance monitoring. It is related to the processing of conflicting inputs (Yeung & Cohen, 2006). ERN/Ne amplitude was discussed to reflect the processing of relevant information, while stimulus-locked N2 amplitude (peaking 200-400 ms post-stimulus, localization in the ACC) was related to the processing of flanking information (Yeung et al., 2004; Falkenstein et al., 1991). Botvinick (2007) extended the conflict monitoring theory in an integrative approach. Hereby, the ERN/Ne was considered as an aversive event, provoking avoidance, according to reinforcement learning principles.

However, both described theories imply increased ACC activity related to cognitive control and behavioral adaption. The lateral prefrontal cortex interacts with the ACC in behavioral monitoring and guiding compensatory systems (Gehring & Knight, 2000). To assess the fast, distinct performance monitoring processes, ERP measures were assessed within **Study 2** (ERN/Ne, N2). The additional fNIRS measurement allowed investigation of compensatory dlPFC activity.

At the behavioral level, prolonged response times in trials after errors compared to trials following a correct response, were termed post-error slowing (PES; Rabbitt, 1966). Larger ERN/Ne amplitudes were related to increased PES (Gehring et al., 1993), however, this pattern seems to be inconsistent (Gehring & Fencsik, 2001). Additionally, PES was related to conscientiousness and impulsivity (Hill et al., 2016; Soshi et al., 2015), which indicates that behavioral adaption is not only driven by state variables but that trait variables have to be considered as well. This raises the question, if the ERN/Ne is a marker for impairments in error-adaption. Or, in other words: performance monitoring (ERN/Ne, N2) is discussed as a measure for deficient transition from automatized to deliberative behavior. To elucidate this question, potential performance-monitoring modulators explaining inter-individual differences will be considered in the following.

### *2.1.2 Performance monitoring (ERN/Ne, N2) modulators*

The extended conflict monitoring hypothesis involves ACC modulations by personality or current motivational states via inputs from other PFC regions, the OFC, ventral striatum and amygdala (Segalowitz & Dywan, 2009). There is even evidence for ERN/Ne amplitude increases with

age (Wiersema et al., 2007). Additionally, there are sex-specific effects on ERN/Ne (Larson et al., 2011) and N2 (Clayson et al., 2011) amplitudes. Therefore, both modulators were equally distributed between both groups (HD and LD) measured within **Study 2.** Still, there is evidence for state-dependent ERN/Ne modulators: Methylphenidate increased ERN/Ne amplitude (Barnes et al., 2014), while acute alcohol ingestion diminished ERN/Ne amplitude (Nelson et al., 2011). Increased task difficulty was related to increased N2 and ERN/Ne amplitudes, which was interpreted as increased need for cognitive control mechanisms (Schroder et al., 2012). ERN/Ne amplitude modulations were discussed as adaptive post-conflict signals for the need to recruit conflict control, depending on the conflict of previous stimulus-type (Larson et al., 2012). Even embodiment-evoked positive emotions decreased ERN/Ne amplitude (Wiswede et al., 2009). The aforementioned ERN/Ne modulators strongly differ according to their endurance. Nevertheless, the ERN/Ne was discussed as a potential endophenotype (Olvet & Hajcak, 2008). Per definition, endophenotypes are associated with a disease, are heritable and state-independent. According to that definition, internalizing disorders like anxiety (e.g. Weinberg et al., 2015) or obsessive compulsive disorders (Gehring et al., 2000) were related to increased ERN/Ne amplitudes, while externalizing symptoms like substance abuse were related to blunted ERN/Ne amplitudes (Franken et al., 2007, Hall et al., 2007). Although there is evidence for state-dependent modulations of the ERN/Ne, some authors discuss relations of ERN/Ne amplitudes to the predisposition for psychopathologies. For a better understanding of the functional meaning of this assumption, the focus will be narrowed to SUD in the following. SUD features will be described, involving the aforementioned performance-monitoring characteristics.

### 2.2 Features of addictive behavior

SUD is a serious chronic disorder, listed in the ranking as the 8$^{th}$ death cause globally, e.g. alcohol dependency having a mortality rate of about 4%. Even after years of abstinence, SUD patients recover old consumption patterns fast after a relapse. This clinical phenomenon is established by the persistence of the addiction memory and impairments in cognitive control. Diagnostic criteria reflect this phenomenon as loss of control over the beginning, duration and the ending of the consumption (ICD-10, WHO, 1992). Drugs of abuse have neurotoxic effects, damaging neuroanatomic structures. For instance, heavy alcohol consumption is related to frontal-lobe volume loss in alcoholics (Pfefferbaum et al., 1997). This is an important point, but as within this work there was no anatomical imaging, this introduction is restricted to functional alternations. To control this factor, HD were considered instead of patients with alcohol dependency. This allows the

focus on functional alternations of the brain, without severe impairments due to brain volume loss. Noel et al. (2013) described abnormal functioning in one or more of three cognitive systems in SUD:

1) Amygdala-striatum (automatic, habitual, salient behaviors)
2) PFC (self-regulation and forecasting consequences of own behavior)
3) Insula (perception of interoceptive signals and processing of emotional processes like craving, influencing decision-making and impulse control processes related to uncertainty, risk and reward).

However, NIRS and tDCS are restricted to the outer layers of cortical regions. Therefore, this work focused on the PFC (2). Indirectly, the amygdala-striatum network was measured by its afferences to the OFC (1). A further indirect measure of amygdala and striatum activation was the heart-rate variability (HRV) within **Study 4** (1). Insula activity was indirectly measured by reports of subjective craving (3). It is important to keep in mind that a crucial characteristic of addiction affects the automatized and fast subcortical network, which could not be directly assessed within this dissertation project. The prefrontal cortex as counterweight for this process was assessed. Therefore, this work focused on the interplay of the automatized system with executive functioning, especially PFC involvement.

Addictive behavior is featured by decision making deficits. The deficit in withstanding immediate benefits of drug consumption in order to reach long-term goals or prevent serious harm (health problems, job loss and problems in social relationships) is characteristic for SUD. This feature is related to impairments in executive functioning (review: Jentsch & Taylor, 1999, Koob & Volkow, 2010, Perry & Caroll, 2008, Wilcox et al., 2014). According to the dual-system perspective on addiction, behavioral control is determined by the imbalance of automatized behavior and cognitive control (McClure & Bickel, 2014). Reduced striatal dopamine functioning is related to diminished dlPFC and ACC functioning, resulting in impairments in cognitive and behavioral control, impairing decision making and response inhibition (Volkow et al., 2003; van Holst & Schilt, 2011). Diminished error-monitoring contributes to this deficiency and is therefore investigated in SUD (review: Luijten et al., 2014). Impairments in executive functioning have already been discussed in high-risk consumers without dependency: There is evidence for performance-monitoring impairments at a pre-pathological stage in HD, in terms of reduced response inhibition (Papachristou et al., 2012).

On the other hand, increased error-monitoring was found in alcohol-dependent patients with anxiety comorbidity (Schellekens et al., 2010), which was discussed as a subpopulation in alcohol dependency. But there is even evidence for increased ERN/Ne amplitudes in abstinent patients with alcohol dependency. This result was discussed as an effortful compensation, allowing behavioral

results comparable to controls (Padilla et al., 2011). Equivalently in HD, there is evidence for increased ERN/Ne amplitudes in a sample without differences to controls in behavioral outcomes (Smith et al., 2015). Within **Study 2,** dlPFC activity was measured as a potential ROI for compensatory activity. Nevertheless, constraints in compensation should be considered. The "resource depletion model" states that self-control is a limited resource and that inhibition of alcohol drinking interferes with other cognitively demanding capacities (Muraven & Baumeister, 2000). The "Cognitive processing model of craving" states that in craving-eliciting situation, interference with other cognitive tasks occurs (Tiffany & Conklin, 2000). Therefore, cue-reactivity and error-monitoring interference were analyzed within **Study 2**. There is evidence for impairments in executive functioning especially in alcohol contexts (Wilcox et al., 2014). For this work, the focus on the context is highly relevant. Therefore cue-reactivity effects need to be considered to allow a better understanding of the interaction with cognitive control.

*Cue-reactivity*

Cue-reactivity is established by the mechanisms of operant and classical conditioning (Carter & Tiffany, 1999; Hammerslay, 1992). Although the specific mechanism of action differs across substances of abuse, every intoxication activates the dopaminergic mesocortical and mesolimbic system. Conscious experience of drug intoxication, drug incentive salience, craving and compulsive drug administration is processed in the mesocortical system (involving PFC, OFC, ACC, as examples for the structures assessed within this work). Structures that were not directly assessed within this work are: Nucleus accumbens, amygdala and hippocampus. These structures mediate the rewarding intoxication effects (Goldstein & Volkow, 2002). Interestingly, those regions are fundamental for conditioning learning, which implies the biological basics for the evolvement of cue-reactivity. During intoxication, initially neutral cues become a conditioned stimulus by means of classical conditioning. The conditioned response is reflected as cue-reactivity thereafter. Smoking-cue induced craving was related to the extended visual system, superior and middle temporal gyrus, precuneus, posterior and anterior cingulate, PFC, OFC and dorsal striatum (Engelmann et al., 2012) and was correlated to a trait variable, namely impulsivity (Bourque et al., 2013).

The subcortical sensitization (increased salience) of drug cues relies on neuronal adaption from the dopaminergic system and the hyperactivation of the reinforcement system in the context of drug cues. During the development of SUD, salience of natural reinforcers declines, while the incentive value and salience of the drug increases (Everitt & Robbins, 2005). Repeated drug consumption leads to neuro-adaptions in the ventral striatum and ventral tegmental area resulting

in decreased dopamine secretion, which explains the decrease in the reinforcing value of natural reinforcers (Volkow et al., 2009). Although we did not assess subcortical structures directly within the four described studies, those alterations are fundamental to the understanding of cue-reactivity effects (e.g. Yalachkov et al., 2012, Kühn & Gallinat, 2011).

Cue-reactivity manifests itself at independent levels (Carter & Tiffany, 1999; Drummond, 2001): an autonomic component reflecting increased arousal (e.g. heart-rate, sweating) at a conscious level, reflected in subjective "craving", and at an automatized behavioral level (approach behavior). Interestingly, Szegedi et al. (2000) revealed that only 22% of an alcohol-dependent population showed both subjective and physiological features of cue-reactivity during alcohol cue-exposure. 42% showed only the physiological reaction, without subjective craving, and 31% did not show any sign of cue-reactivity. An overview revealed that only approximately one third of SUD patients depicted craving and physiological response during alcohol cue exposure (Carter & Tiffany, 1999, Drummond, 2001). It is therefore important to include different levels of cue-reactivity in experiments. In **Study 3** and **Study 4**, prefrontal activity was assessed in addition to craving ratings. In **Study 4**, HRV was analyzed to assess the time-course of the autonomic level.

To explore cue-reactivity in experimental designs, different paradigms are common: In fMRI studies, olfactory, gustatory and visual cues can be used to measure activity changes in the brain (for a review see Courtney et al., 2016; Schacht et al., 2013). Those studies revealed an interconnected network relying on dopaminergic, GABAergic, opioid and glutamatergic pathways in the ventral tegmental area (VTA), ventral striatum, ventromedial prefrontal cortex (vmPFC), amygdala, lateral hypothalamus and the hippocampus (review: Jentsch & Taylor, 1999).

An advantage of investigations of visually evoked cue-reactivity is that it can be easily applied within the laboratory and it can be combined with additional tasks (cf. **Study 2**). The LPP (late positive potential, a centro-parietal ERP, 400–700 ms post-stimulus), is related to "motivated attention" evoked by emotional content (Schupp et al., 2000). This amygdala induced activation of the visual cortex (Bradley et al., 2003) was analyzed in **Study 1.** A problem with such standardized cues is the short duration and the lack of validation of cues with longer presentation (Schacht et al., 2013).

Another approach to evoke cue-reactivity is in vivo cue-exposure, which provides increased cue salience through the activation of multiple sensory modalities. However, the cost of this improvement is increased noise, related to less standardization and increased variability across subjects. Furthermore, carryover-effects complicate control conditions (Monti et al., 1987). Therefore, in **Study 3** and **Study 4**, cue-reactivity was elicited in smokers during in vivo smoking cue-exposure, without a within-subject control condition.

It is important to establish valid cue-reactivity assessments even for the treatment of SUD: Craving was related to relapse rates in alcohol dependent patients (Oslin et al., 2009) and smokers (Shiffman et al., 1996). Likewise cue-induced striatal and orbitofrontal responses were related to increased relapse risk (Baler & Volkow, 2006; Everitt & Robbins, 2005; Janes et al., 2010). Still there is a great variance across studies considering the predictive value of cue-reactivity markers for relapse. Therefore, methodological issues related to such inconsistencies will be further described in the general discussion. But first, after describing the severe dysregulations in SUD, the state of the art for its treatment needs to be introduced.

### 2.3 SUD treatment

SUD treatment involves detoxification and relapse prevention, the latter being further described. Approaches for relapse prevention involve bio-psychosocial and pharmacologic treatments, yet clinical trials reflect moderate outcomes (Dutra et al., 2008). McLellan et al. (2000) reviewed that only 40-60% of treatment-seeking subjects with substance dependency were abstinent in a 1-year follow-up. Including subjects attempting to quit without treatment was even worse, revealing 72-90% one-year relapse rates in smokers (Norregaard et al., 1992; Ferguson et al., 2005).

Statistics reveal the need for a better understanding of the obstacles that occur, even after the decision to stop consumption. Patients are often advised to avoid cue-reactivity triggering situations. Especially for legal drugs, like cigarettes and alcohol, this avoidance is impossible. Besides its practical consideration, this approach has a theoretical shortcoming: Clinicians implicitly state that the patient would not be able to inhibit automatized cue-reactivity deliberately. But this reinforces the already reduced self-efficacy in SUD. This perspective, however, results from every day clinical routine, from patients reporting automaticity of behavioral choices. However, inter-individual variability in cue-reactivity might likewise be affected by perceived self-efficacy and positive outcome expectancy (Glautier & Tiffany, 1995). Individuals with decreased self-efficacy and high expectancy of positive drug effects would be expected to reveal increased cue-reactivity. Accordingly, cue-exposure treatment aims at an increase of self-efficacy (Rohsenow et al., 1995).

As described in the cue-reactivity chapter, the persistence of cue-reactivity aggravates SUD treatment. Considering the resource depletion model, indeed, behavioral inhibition is limited. Yet, a comparison to treatment approaches in anxiety disorders, which are likewise established via conditioning processes, indicates that symptoms are maintained by avoidance. In cognitive behavioral therapy, it is state of the art to conduct expositions. Against this background, it seems to

be fundamental to SUD treatment to involve cue-exposure. However, practically, this approach is not yet an inherent part of relapse prevention programs. Still, there are some challenges for cue-exposure in SUD patients, that will be addressed in the following. As extinction learning is the prerequisite for the efficacy of exposition, it needs to be addressed first.

### *2.3.1 Extinction learning*

As addiction memory evolves by the principles of operant and classical conditioning, its reversal is related to extinction learning (Myers & Carlezon, 2010). The occurrence of a conditioned response is diminished by repeated presentation of a conditioned stimulus without reinforcement. Extinction learning enables learning of new contingencies via inhibition of an old response. This extinction learning occurs when context changes, when a response is no longer adaptive. It reflects the unlearning of the significance of a stimulus (Quirk et al., 2006). The conditioned response is not erased, but rather suppressed in a context and time dependent manner (Bouton, 2002). Spontaneous recovery (Pavlov, 1927), reinstatement (Rescorla & Heth, 1975) and renewal effects (Bouton & Ricker, 1994) are observations of the re-occurrence of a conditioned response, indicating the retention of the old stimulus-response connections, even after long periods without behavioral occurrence of the conditioned response. The occurrence of a conditioned response is suppressed by inhibitory connections from the prefrontal cortex to subcortical regions (Myers & Carlezon, 2010).

A problematic feature of extinction for SUD treatment is a high context dependency and poor contextual generalization (Collins & Brandon, 2002). This requires an increase in ecological validity for extinction learning measurements in SUD. The measurement of prefrontal hemodynamic activity during extinction learning of drug-related cues was the target of **Study 3** and **Study 4**. This paradigm is investigated for relapse prevention in SUD and is referred to as cue-exposure therapy (CET).

*2.3.2 Cue-Exposure Therapy (CET)*

An important goal of this intervention is the disruption of habitual drug-seeking behavior. A review on CET efficacy (Martin et al., 2010) between 2002 and 2009 revealed 16 studies of which four tested efficacy in a clinical trial. In 3 of those 4 trials, CET was equal to the control therapy. A common problem of those studies is the low statistical power due to small sample sizes. However, there is evidence for reduced activity in the ventral striatum after 9 CET sessions in alcohol-dependent patients (Vollstädt-Klein et al., 2011). Results are limited, as beneficial treatment effects were not correlated with findings at the behavioral level (relapse, drinking behavior). Most frequently, decreases in ventral striatum activity correlated with CET treatment effects (Schacht et al., 2013). However, those results stem mostly from ROI analyses interrogating limbic structures.

Another problem in such studies is the variety of CET implementation across studies. A common approach is the gradual intensify the examination of the drug cue. In the case of alcohol: the confrontation begins with a visual inspection of the alcoholic drink, then the bottle is touched, smelled and finally poured it into a glass followed by individual attempts to amplify craving. Mood induction before in vivo CET is sometimes applied to increase craving (e.g. audiotaped conflicts, imagination; cf. Lindenmeyer, 2005).

Furthermore, there is even heterogeneity in the dependent variables across studies investigating CET. As described earlier, there are inter-individual differences of cue-reactivity manifestations. Most studies use craving as dependent variable, neglecting other cue-reactivity dimensions such as physiological reactions or measures of overt behavior like relapse rates. Even the definition of relapse is not fine-grained enough, as intensity of relapse (how many drinking events, how many drinks) is often insufficiently described. A further problem in comparing CET studies is the inconsistency of applied sessions across studies. Unrod et al. (2013) highlighted the importance of repetition for extinction learning processes. They found craving reductions within and between 6 CET sessions in smokers. Although craving was reduced since the first session, differential reactivity to neutral vs. smoking-related cues was significant during the sixth session.

For the evaluation of CET efficacy, assignment criteria for the intervention need to be additionally involved. Shiffman et al. (2013) reported a significant number of non-responders to CET in patients without differential reactivity to smoking and control cues at baseline. Likewise, Unrod et al. (2013) reported 26% non-responders. A shortcoming of this study was the one-dimensional cue-reactivity assessment (craving). Still, the number is comparable to the amount of alcohol dependent subjects without cue-reactivity markers (31%; Szegedi et al., 2000). These results highlight the importance of a multidimensional cue-reactivity baseline assessment to identify

markers with prognostic value for CET efficacy. Furthermore, the high context sensitivity of extinction learning needs to be considered when investigating CET efficacy. The relation of prognostic value of cue-reactivity markers to the ecological validity of the cue-reactivity measurement needs to be approved.

From a biological and psychological perspective, improvements in relapse prevention after CET in SUD are expected, which is however not approved by empirical evidence. This indicates the need for a better understanding of the underlying mechanisms and accordingly the optimization of the intervention. Reduced dlPFC activation is a deficit in SUD which is problematic for a treatment based on dlPFC activity (extinction learning). One approach to overcome this problem is the focus on the neuromolecular basis of extinction processes. The activity of NMDA-receptors during inhibitory control generated in prefrontal regions is the prerequisite for neuronal plasticity enabling extinction learning. Therefore, effects of drug enhancement on receptor functioning by direct current during CET have been reviewed (Myers & Carlezon, 2012). Results were not striking; therefore, within this work, another method for local amplification of NMDA-receptor functioning was applied: anodal tDCS. In **Study 4**, immediate tDCS effects on prefrontal activity during a CET session were analyzed. Application above the dlPFC aimed at the enhancement of executive functioning. The use of cognitive enhancers during CET has been already suggested (Dhonnchadha & Kantak, 2011). Therefore, enhancement strategies for executive functioning will be reviewed in the next section.

### *2.3.3 Enhancement of executive functioning in the treatment of SUD*

Impairments in attention, working memory and response inhibition in SUD were related to decreased dlPFC activity (Sofuoglu et al., 2013; Koob & Volkow 2010). Therefore, the dlPFC is a convenient target region in the addiction network (Duka et al., 2011). One approach to increase dlPFC activity is to apply cognitive strategies like reappraisal. Kober et al. (2010) found that increased dlPFC activity during cognitive regulation of craving was related to ventral striatum activity reductions in smokers. Further methods for cognitive enhancement are behavioral cognitive training or direct regulation of activity within the dlPFC via neurofeedback or non-invasive brain stimulation techniques (Eriquez-Geppert et al., 2013). Still, transfer effects to critical situations such as cue-exposure have to be investigated. In the next paragraph, tDCS will be further described as an example for non-invasive brain stimulation aiming at the enhancement of dlPFC functioning in SUD.

### *2.3.4 Non-invasive brain stimulation*

A meta-analysis of dlPFC stimulation with non-invasive brain stimulation (tDCS and TMS) to reduce craving revealed a medium (Hedge's *g* = 0.476) effect size (Jansen et al., 2013). Although data is promising, there are several shortcomings of the reviewed studies: Studies in this field are often preliminary in nature and rely on small sample sizes. There is no consistency in the number of applied tDCS sessions, duration of stimulation, intensity, montages and the context of application (in rest, during a task).

There is some encouraging data from a Phase-II randomized clinical trial in outpatients with alcohol dependency (Klauss et al., 2014). Bilateral tDCS over the dlPFC on five consecutive days increased the perception of quality of life, but involved no significant reduction of craving ratings. At 6-month follow-up, 50% of patients receiving real tDCS and 11.8% of sham stimulated patients were alcohol abstinent. Still, this data needs replication as the sample size was small (n=33). There is evidence for immediate stimulation effects within one session (Da Silva et al., 2013) and findings show a significant craving reduction not before the seventh session (Politi et al., 2008). More studies are needed to find the most efficient electrode montage and stimulation parameters for the clinical use in SUD treatment. In the following, three promising studies guiding tDCS parameters in **Study 4** will be presented**.**

Anodal tDCS of the dlPFC diminished craving in subjects with nicotine (Fregni et al., 2008; Boggio et al., 2009) and alcohol (Boggio et al., 2008) dependency. Fregni et al. (2008) stimulated 24 heavy smokers with anodal left vs. anodal right dlPFC vs. sham stimulation (1 session, 20 min duration, 2 mA). Boggio et al. (2008) revealed craving reduction during video cue-exposure after active randomized tDCS (2 mA, 20 min) in 13 alcohol dependent patients. Boggio et al. (2009) found a reduction in craving and number of cigarettes smoked in 27 smokers in the active stimulation group after five tDCS sessions.

There is first evidence of tDCS-induced craving reduction. Two models to explain this effect on craving reduction, will be presented in the following: One hypothesis is that PFC stimulation mimics drug effects via dopaminergic release in mesostriatal and mesolimbic pathways, inducing craving reductions (Naim-Feil & Zangen, 2013). Another possible mechanism is based on inhibitory effects of dlPFC activation on subcortical regions (VTA, ventral striatum) decreasing cue-reactivity (Diana, 2011). Still, more evidence is necessary to improve our understanding of basic tDCS mechanisms. Nevertheless, summarizing the field of non-invasive brain stimulation reveals promising treatment options that need more evidence for the most efficient application. The application within this work (**Study 4**) investigated merely the convenience of the methods to

contribute to the empirical data required in the field. Within the next section, the aims and hypotheses of all four studies will be summarized.

**2.4 Summarized aims and hypotheses:**

The focus of **Study 1** was to capture visual alcohol cue-reactivity effects on ERP in HD/ LD and their modulation by visual features independent of cue-reactivity.

*Hypothesis 1:* HD reveal cue-reactivity, reflected in increased P100 and LPP amplitudes for alcoholic cues when content (alcoholic vs non-alcoholic) is recognizable.
*Hypothesis 2:* There are no differences between HD and LD in the processing of visual features of the pictures without content information.

The focus of **Study 2** was the effect of cue-reactivity on cognitive control in another sample of HD/LD. The visual beverage cues validated in **Study 1** were integrated into a modified Eriksen Flanker Task to analyze the interactions of cue-reactivity, error-monitoring and cognitive control. Simultaneous fNIRS-EEG measurements provided high temporal resolution to measure fast error-monitoring processes and a good spatial resolution of hemodynamic activity in the prefrontal cortex to localize adaptive effects of cognitive control.

*Hypothesis 3:* Error-monitoring is impaired by alcoholic-cues in HD.
*Hypothesis 4:* Deficient error-monitoring is compensated by prefrontal activity in HD.

The focus of **Study 3** was the increase of ecological validity of the cue-reactivity measurements using in vivo cue-exposure in smokers. Within this study, prefrontal cortical hemodynamic activity (using fNIRS) and craving was measured in smokers/non-smoking controls.

*Hypothesis 5:* Cue-reactivity is elicited in smokers, not controls. This can be measured in craving ratings and increased OFC activity in smokers.
Hypothesis 6: Inhibition of smoking is related to increased dlPFC activity in smokers.

The aim of **Study 4** was to investigate the immediate tDCS effects on cognitive control during in-vivo cue-exposure (cf. **Study 3)** in smokers. HRV was an additional measure of autonomic activity. Feasibility of simultaneous tDCS and fNIRS application during the in-vivo context was investigated.

*Hypothesis 7:* Cue-reactivity markers (HRV, craving, OFC activity) are reduced during tDCS compared to sham stimulation.

*Hypothesis 8:* tDCS increases cognitive control (dlPFC activity).

Those studies provide insights into neurobiological markers of cue-reactivity, reflecting automatized behavior and their interferences with cognitive control, involved in deliberative decision making, in samples of regular alcohol drinkers (**Study 1, Study 2**) and smokers (**Study 3, Study 4**). After describing each of the four studies individually, conclusions will be integrated and discussed in terms of their value for addiction research and treatment. In **Study 1** and **Study 2**, basic features affected by cue-reactivity were assessed. Still, those effects are related to automatic processing, requiring a transition to conscious experience for its reversal. Therefore, the concept of mindfulness was considered in the following study designs (**Study 3**, **Study 4**).

## 2.5 Statement of contributions:

**Study 1:**

Kroczek, A. M., Haeussinger, F. B., Hudak, J., Vanes, L. D., Fallgatter, A. J., & Ehlis, A.-C. (2018). Cue Reactivity Essentials: Event-Related Potentials During Identification of Visual Alcoholic Stimuli in Social Drinkers. *Journal of Studies on Alcohol and Drugs, 79*(1), 137–147.

The project was presented in a practical seminar lectured by A.-C. Ehlis and hosted by the psychological institute (Prof. M. Hautzinger). The participants learned about psychophysiological methods (EEG) during the practical involvement in data acquisition in a small group instructed by A.M. Kroczek. L.D. Vanes was participant in the seminar writing an excellent report of the study project and therefore was involved in writing the manuscript. The study was conducted at the Department of Psychiatry and Psychotherapy, Tübingen (Head: A. J. Fallgatter). A.M. Kroczek contributed significantly to study conceptualization, instructions and practical help with data acquisition, analysis, interpretation and discussion and contributing major parts to writing.

| | |
|---|---|
| A. M. Kroczek: | study design, data acquisition, data analysis, interpretation, writing |
| F. B. Haeussinger: | providing Matlab-scripts for the analysis of behavioral data |
| Hudak, Justin: | critical revision |
| Vanes, L.D: | data acquisition, writing |
| Fallgatter, A.J. | conceptual input, critical revision |
| Ehlis, A.-C. | conceptual input, writing, interpretation, critical revision |

**Study2:**

Kroczek, A. M., Haeussinger, F. B., Hudak, J, Fallgatter, A. J., & Ehlis, A.-C. (submitted). *Effects of Visual Alcoholic Cues on Error-Monitoring, Conflict Processing and Cognitive Control in Social Drinkers – A combined fNIRS-EEG study.*

The project was funded by the Centre for Integrative Neuroscience, CIN (Pool Projekt Nr. 2010-11; Förderzeitraum: 2011-2013). The project was conceptualized by A.-C. Ehlis and A.J. Fallgatter. A.M. Kroczek joined the project as doctoral student. A.M. Kroczek contributed significantly to the practical realization of the project. Beginning with the data acquisition, the analysis, interpretation and discussion were provided by A.M. Kroczek. A.M. Kroczek wrote vast parts of the manuscript completed by input from A.-C. Ehlis.

| | |
|---|---|
| A. M. Kroczek: | data acquisition, data analysis, interpretation, writing |
| F. B. Haeussinger: | providing Matlab-scripts for the analysis of behavioral and fNIRS data |
| Hudak, Justin: | critical revision |
| Fallgatter, A.J. | conceptualization, critical revision |
| Ehlis, A.-C. | conceptualization, writing, interpretation, critical revision |

**Study 3:**

Kroczek, A. M., Haeussinger, F. B., Fallgatter, A. J., Batra, A., & Ehlis, A.-C. (2017). Prefrontal functional connectivity measured with near-infrared spectroscopy during smoking cue exposure. *Addict Biol, 22(2),* 513-22.

The project was presented in a practical seminar lectured by A.-C. Ehlis and hosted by the psychological institute (Prof. M. Hautzinger). The participants learned about psychophysiological methods (fNIRS) during the practical involvement in data acquisition in a small group instructed by A.M. Kroczek. The study was conducted at the Department of Psychiatry and Psychotherapy, Tübingen (Head: A.J. Fallgatter). A.M. Kroczek contributed significantly to study conceptualization, instructions and practical help with data acquisition, analysis, interpretation and discussion and writing major parts of the manuscript (completed by input from A.-C. Ehlis).

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|---|---|
| A. M. Kroczek: | study design, data acquisition, data analysis, interpretation, writing |
| F. B. Haeussinger: | providing Matlab-scripts for the analysis of behavioral and fNIRS data |
| Fallgatter, A.J. | conceptual input, critical revision |

| | |
|---|---|
| Batra, A. | conceptual input, critical revision |
| Plewnia, C. | conceptual input, critical revision |
| Ehlis, A.-C. | conceptual input, writing, interpretation, critical revision |

**Study 4:**

Kroczek, A. M., Häußinger, F. B., Rohe, T., Schneider, S., Plewnia, C., Batra, A., Fallgatter, A. J., & Ehlis, A.-C. (2016). Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure. *Drug and Alcohol Dependence*, *168*, 123-127.

The project was presented in a practical seminar lectured by A.-C. Ehlis provided by the psychological institute (Prof. M. Hautzinger). The participants learned about psychophysiological methods (fNIRS) during the practical involvement in data acquisition in a small group instructed by A.M. Kroczek. The study was conducted at the Department of Psychiatry and Psychotherapy, Tübingen (Head: A.J. Fallgatter). A. Batra and C. Plewnia were critical advisors contributing to the discussion due to their field of expertise. A.M. Kroczek contributed significantly to study conceptualization, instructions and practical help with data acquisition, analysis, interpretation and discussion and writing major parts of the manuscript (completed by input from A.-C. Ehlis).

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|---|---|
| A. M. Kroczek: | study design, data acquisition, data analysis, interpretation, writing |
| F. B. Haeussinger: | providing Matlab-scripts for the analysis of behavioral and fNIRS data |
| Sabrina Schneider: | Contribution of neuroanatomical assignment |
| Tim Rohe: | implementation of automatized wavelet-artifact-rejection |
| A. Batra | critical revision |
| C. Plewnia: | critical revision |
| Fallgatter, A.J. | conceptual input, critical revision |
| Ehlis, A.-C. | conceptual input, writing, interpretation, critical revision |

## 3. Study 1: Cue-Reactivity Essentials: Event-related Potentials during Identification of Visual Alcoholic Stimuli in Social Drinkers

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Kroczek, A. M., Haeussinger, F. B., Hudak, J., Vanes, L. D., Fallgatter, A. J., & Ehlis, A.-C. (2018). Cue Reactivity Essentials: Event-Related Potentials During Identification of Visual Alcoholic Stimuli in Social Drinkers. *Journal of Studies on Alcohol and Drugs, 79*(1), 137–147.

**3.1 Abstract**

**Objective:** Cue reactivity is an automatic reaction to alcohol-related cues, contributing to the maintenance of drinking behavior and relapse in alcohol dependency. The identification of valid cue-reactivity features is a prerequisite for its clinical application. We were interested in the effects of visual features of alcohol cues (e.g., color) on cue reactivity. Assuming its development at a pre-pathological stage, we analyzed cue reactivity in HD, with LD as controls. We investigated whether cue reactivity was independent of visual features at an attentional (P100) and a motivational level (LPP). **Method:** ERPs (P100, LPP) were analyzed during a visual beverage classification task in HD and LD (*N* = 34 university students). Photographs of beverages were classified as alcoholic or nonalcoholic. Two additional stimulus sets depicted unrecognizable scrambled visual information and recognizable black silhouettes of the original beverages. Analysis of contrast waves inferred content (unrecognized scrambled trials subtracted from original) and color information (recognized shape trials subtracted from original) during visual processing. Linear regression was used to predict Alcohol Use Disorders Identification Test (AUDIT) scores from ERPs. **Results:** In HD, alcoholic-content LPP and P100 latency increased compared with nonalcoholic cues. Linear regression for alcohol content condition in the overall sample revealed shorter P100 latency and increased LPP amplitude predicting AUDIT scores. None of those effects were significant in the visual-feature control condition. **Conclusions:** Alcohol cue-reactivity in HD was related to faster early attentional processes and motivational salience. The effect occurred independently of visual features in the pictures.

(*J. Stud. Alcohol Drugs, 79,* 000–000, 2018)

**3.2. Introduction**

Exposure to alcohol-associated cues can evoke reactions in individuals with alcohol dependency (Drummond, 2000) at subjective (e.g., craving), physiological (e.g., skin conductance), and behavioral levels (substance-seeking/relapse; Garland et al., 2012). This automatic response, termed *cue reactivity,* is related to relapse risk in alcohol dependency (Papachristou et al., 2014). The addiction network is formed by repeated alcohol consumption, strengthening connections of the reinforcing immediate alcohol effect to cue features (e.g., sight, smell) and context information (e.g., environment, mood). Cue reactivity is the manifestation of the activated addiction network evolving by means of conditioning processes at a pre-pathological stage (Tiffany, 1995).

In studies focusing on the cognitive factors of cue reactivity (Field & Cox, 2008), attentional bias to alcohol cues was increased in HD at a behavioral level (Field et al., 2004; Townshend & Duka, 2001). Attentional bias is considered an important factor in the development and maintenance of

addictive behaviors (Field & Cox, 2008; Townshend & Duka, 2001). Analyses of brain responses underlying cue reactivity provide a better understanding of affected processing steps. The visual P100 is a fast ERP generated within extrastriate visual regions (Mangun & Hillyard, 1991), a perceptive level of visual processing affected by emotional stimuli (Herrmann et al., 2005). Another ERP, the LPP, arises from reciprocal frontal and occipital-parietal regions, approximately 400 ms after the presentation of motivationally salient emotional stimuli (Hajcak et al., 2009; Schupp et al., 2000). Furthermore, arousal to emotional stimuli has been linked to LPP (Hajcak & Nieuwenhuis, 2006).

Cue reactivity at a perceptual level (indexed via P100 amplitude) was found in HD (Petit et al., 2012a) and individuals low in alcohol sensitivity (Shin et al., 2010). Binge drinkers show an increase in attentional allocation to alcohol-stimuli during a visual oddball task (Petit et al., 2012b), whereas individuals low in alcohol sensitivity show similar behavior during a visual dot probe task (Shin et al., 2010). Such findings indicate increased attention to alcohol-related stimuli in high-risk participants (Herrmann et al., 2001). But studies are inconclusive; for example, there was no such effect observed in detoxified alcoholics (Matheus-Roth et al., 2016). The LPP is relevant for addiction research, as it reflects incentive salience, which is attributed to drug cues via conditioning processes (Franken et al., 2008). Accordingly, motivated attention to drug-related cues in active cocaine users resembled the reaction to stimuli with high incentive value, such as emotional stimuli (Dunning et al., 2011). The LPP as a marker for cue reactivity has also been discussed in a meta-analysis in terms of increased motivated attention (Littel et al., 2012).

Although attentional bias to substance-related cues seems to have increased motivational significance in high-risk populations and patients with SUD, basic visual features such as color are also known to affect ERPs (Cano et al., 2009; Olofsson et al., 2008; Rozenkrants et al., 2008). Therefore, we wanted to explore whether neurophysiological cue-reactivity markers reflect stimulus content or basic visual features.

We dissociated content information (alcohol vs. nonalcohol) from visual features such as color and brand labels, comparing original pictures to their unrecognizable scrambled counterparts. Equivalently, effects of visual features were analyzed by a comparison of recognizable black silhouettes with original beverage pictures. We expected cue reactivity in the alcohol content condition in HD, whereas visual-feature control should be independent of cue type (alcoholic vs. nonalcoholic). In particular, we expected increased attentional bias (P100) and incentive salience (LPP) related to alcoholic content in HD. We did not expect any effect of cue type in the visual-feature control condition or content condition in LD.

### 3.3. Methods

*3.3.1 Participants*

Thirty-nine healthy participants (university students, ages 20–35 years) took part in the experiment. The Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993) was used to split the sample into HD and LD (HD cutoff score: female, 5; male, 8; Neumann et al., 2004). Five participants were excluded because of heavy artifacts in the EEG. In the final sample ($n$ = 34), there was no difference in age, $t(32) = 0.70$, $p = .49$, between the group of 16 LD ($M_{age}$ = 24 years, $SD$ = 3) and 18 HD ($M_{age}$ = 25 years, $SD$ = 3) or gender (HD: 10 female, 8 male; LD: 8 female, 8 male; $\chi^2$ = 0.105 $p = .746$). See Table 1 for descriptive statistics. Participants had normal or corrected-to-normal vision. They took part in the experiment on a voluntary basis after informed written consent was given. ICD-10 criteria (World Health Organization, 1992) were used to exclude alcohol dependency. The study was approved by the Ethics Committee of the Faculty of Medicine at the University Hospital of Tübingen and all procedures were in line with the Declaration of Helsinki in its latest version.

*3.3.2 Stimuli*

The original stimulus set consisted of 20 photographic pictures of common German alcoholic and nonalcoholic beverages, arranged in pairs (alcoholic and nonalcoholic) of best match for valence, arousal, color, and shape. Two additional stimulus sets were created from the original pictures: black silhouettes (shape) and scrambled color information without any further visual features (scrambled). Each of those three stimulus sets contained 10 alcoholic and 10 nonalcoholic pictures, resulting in 60 stimuli in total (Figure 1). The randomized, repeated presentation of beverage shapes and original pictures allowed for improvements in shape classification accuracy within the experiment. Content was analyzed regarding differences in original and scrambled pictures. The visual-feature control condition reflected differences of original and shape pictures.

**TABLE 1.** Alcohol-related group characteristics, *M* (*SD*)

| Variable | HD | LD | Test statistics | *p* |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| AUDIT score | 11 (4) | 4 (2) | $t_{(26)} = 7.03$ | <.001 |
| Alcoholic standard drinks (last 30 days) | 32 (20) | 9 (7) | $t(21) = 4.50$ | <.001 |
| Number of drinking events (last 30 days) | 11 (5) | 4 (2) | $t(24) = 5.59$ | <.001 |
| IDTSA scores (subscales) | | | | |
| Pleasant emotions | 15 (5) | 9 (6) | $t(32) = 3.27$ | .003 |
| Testing personal control | 1 (2) | 0 (1) | $Z = 1.94$ | .168 |
| Urges and temptations | 7 (5) | 4 (4) | $t(32) = 1.92$ | .064 |
| Unpleasant emotions | 4 (3) | 2 (2) | $t(31) = 2.13$ | .041 |
| Pleasant times with others | 16 (5) | 10 (4) | $t(19) = 1.89$ | .074 |
| Social pressure to use | 13 (4) | 8 (5) | $t(26) = 2.71$ | .012 |
| Physical discomfort | 5 (3) | 1 (2) | $t(31) = 4.13$ | <.001 |
| Conflict with others | 2 (2) | 0 (1) | $Z = 2.57$ | .002 |

*Notes:* HD = heavy social drinkers; LD = light social drinkers; AUDIT = Alcohol Use Disorders Identification Test; IDTSA = Inventory of Drug-Taking Situations (Alcohol).

### *3.3.3 Questionnaires*

Participants filled out questionnaires on demographic data and handedness (Edinburgh Handedness Inventory [EHI]; Oldfield, 1971). Drinking motivation was assessed via the Inventory of Drug-Taking Situations (Alcohol) (IDTSA; Lindenmeyer & Florin, 1998). Immediately before and after the EEG measurement, emotional state (using the German version of the Positive and Negative Affect Schedule [PANAS]; Watson et al., 1988) and momentary craving (a single item on a 5-point Likert scale) were assessed. Furthermore, participants reported their consumption of standard alcoholic units during the previous month using a calendar (Timeline Followback Calendar Method; Sobell et al., 2003).

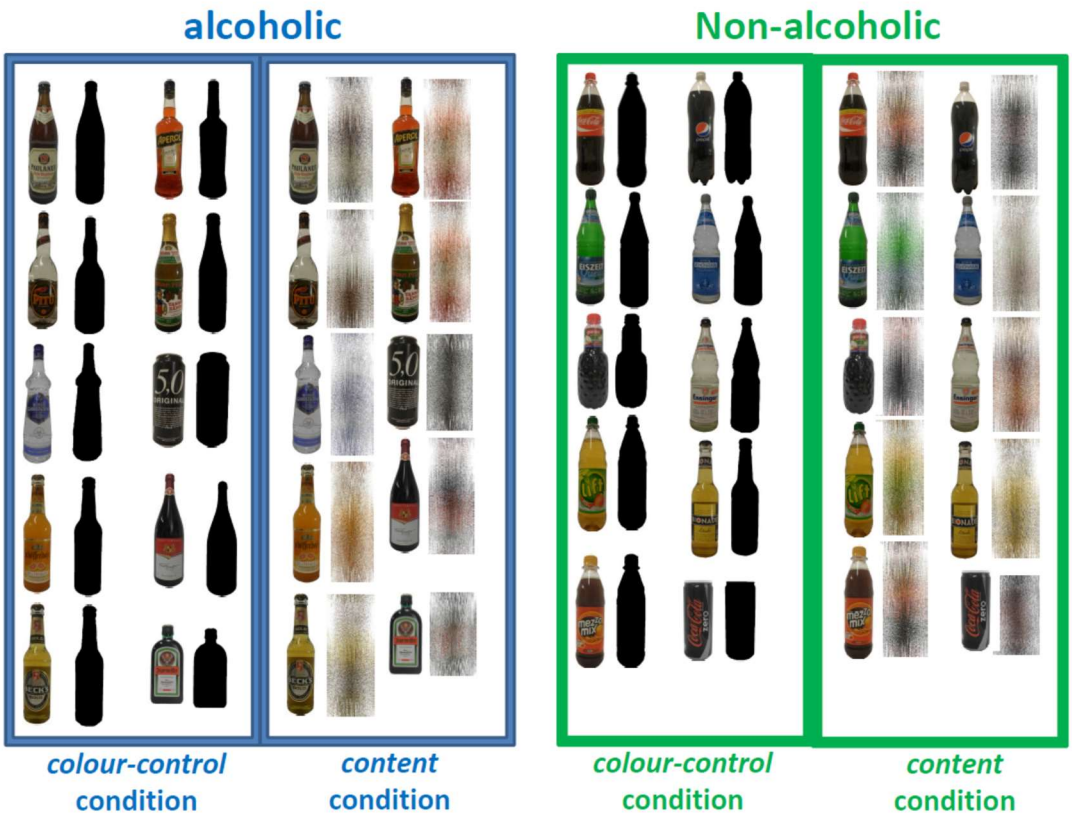


Figure 1 The study used 20 beverage pictures (10 alcoholic vs. 10 nonalcoholic) in three different conditions: original picture, shape, scrambled. Difference waves were calculated for content condition (original minus scrambled) and color-control condition (original minus shape). Pictures involved in each of the four difference wave calculations are depicted. HD = heavy social drinkers; LD = light social drinkers.

*3.3.4 Procedure*

Participants were seated approximately 80 cm from a computer screen and filled out the questionnaires during EEG preparation. The visual beverage identification task was trained during a practice block (10 trials per condition, not involving the stimuli used in the experimental blocks). The total duration of both experimental blocks (150 trials each) was approximately 15 minutes. Each trial began with a 350 ms stimulus presentation (randomized, each stimulus appearing five times). Participants were asked to classify each picture as alcoholic, nonalcoholic, or not recognized "as fast and as accurately as possible" by pressing one of three keys on a standard keyboard. Mappings for alcoholic versus nonalcoholic (left vs. right index finger press) were counterbalanced across participants; "not recognized" responses were always given by pressing the space bar with both thumbs. Empty squares were presented as response options for a maximum of 5,000 ms after stimulus offset. The chosen answer was depicted as a crossed square for 350 ms immediately after

the response. The intertrial interval was determined by a blank white screen (150–500 ms duration). After the experiment, participants rated beverage familiarity, valence, and arousal on a 9-point computer-based Self-Assessment Manikin scale (Bradley & Lang, 1994).

*3.3.5 EEG recordings*

The EEG was recorded from 29 Ag/AgCl ring electrodes positioned according to the international 10-20 system (Jasper, 1958). Recordings were referenced at FCz and re-referenced offline to a common average. FCz was subsequently used as a standard electrode. Two electrodes were placed at the outer canthi of both eyes and an additional electrode was placed beneath the right eye for registration of eye movements. Data were recorded with BrainVision Recorder software (Brain Products, Munich, Germany) at a 500 Hz sampling rate, with impedance values below 5 kΩ and a 0.1–100 Hz bandpass filter.

Data were analyzed using BrainVision Analyzer (Brain Products, Munich, Germany). After independent component analysis–based eye-movement artifact correction, segments including amplitudes below -50 or above 50 µV were rejected from further analyses. A low-pass filter was set to 40 Hz. Segmentation was stimulus-locked (-200 ms to 700 ms) to every Stimulus Type × Condition combination with a 200 ms baseline correction. Six averaged ERP curves were calculated for each participant. For the original and shape trials, signals were extracted for correct classifications. For scrambled trials, "not recognized" responses were extracted due to the lack of correct classifications.

Difference waves were calculated for content (original minus scrambled) and visual-feature control (original minus shape). Content curves allowed dissociation from visual features like color. Visual-feature control curves were controlled for content information (alcoholic vs. nonalcoholic). A measure of alcohol representation strength was calculated by a subtraction of correctly classified alcoholic black shapes from the correctly classified alcoholic original pictures. This variable reflects participants' familiarity with the stimulus set. There was no significant difference between HD ($M$ = 7.5, $SD$ = 7.5) and LD ($M$ = 11.1, $SD$ = 7.5) in alcohol representation strength, $t(30) = 1.03$, $p = .311$. A low number indicates a good representation, independent of visual attributes of a stimulus. A high value indicates a strong dependence on visual features to recognize a stimulus, that is, color or label. To consider the interindividual differences in familiarity of the stimulus set, we used representation strength as a covariate to the analysis of the ERP.

Based on a visual inspection of the grand averages and previous literature, individual P100 peaks were detected semi-automatically in a 90–160 ms stimulus-locked time window (Petit et al., 2012a). P100 peak detection was conducted, identifying the highest point individually for every condition at O1 and O2. For the LPP, the average activity of this broad potential was recorded at Pz in a 450–700 ms time window (Schupp et al., 2012). Participants were included when the minimum number of trials per condition was 12 (Moran et al., 2013).

*3.3.6 Statistical analyses*

SPSS Statistics for Windows, Version 21 (IBM Corp., Armonk, NY) was used for statistical analysis. All reaction time and EEG analyses were conducted on correct trials for the original and shape condition. For the evaluation of the color condition, "not recognized" trials were averaged because of a (stimulus-inherent) lack of correct responses.

Behavioral data were analyzed in a 2 (alcoholic/nonalcoholic) × 2 (original/shape/scrambled) analysis of variance (ANOVA) separately for accuracy and response times. Separate 2 (content vs. visual-feature control) × 2 (alcoholic vs. nonalcoholic) × 2 (group: HD vs. LD) analyses of covariance with representation strength as covariate were used for both ERP analyses. A 2 (positive vs. negative mood) × 2 (before vs. after the measurement) × 2 (group: HD/LD) ANOVA was used for the analysis of PANAS scores. Main effects and interactions with stimulus or group were reported. Wherever necessary, p values were Greenhouse-Geisser corrected. Craving ratings were not normally distributed; therefore, nonparametric testing was applied (Mann–Whitney *U* test analyzing group effects, Wilcoxon Test for time-course).

Four linear regressions of physiological data on AUDIT scores were conducted for each of the four difference waves (alcoholic/nonalcoholic × content/visual-feature control). Within each regression, AUDIT was used as a dependent variable, with P100 latency and LPP mean amplitude as independent variables. Beta values were calculated to analyze the impact of the independent variable on the model in each of the four linear regressions.

### 3.4 Results

#### *3.4.1 Behavioral data*

*Correct classification.* Response accuracy was above chance level in the original (96% correct) and shape (80% correct) trials. Eighty percent of the scrambled trials were classified as "not recognized." The remaining 20% of the scrambled condition indicate guessing, as there was no effect (all *F*s < 1, *p*s > .05) of group (HD/LD) or stimulus type (alcohol/nonalcohol) on response (alcohol/nonalcohol).

*Reaction times.* A Condition × Stimulus Type interaction, $F(2, 64) = 4.76$, $p = .012$, $\eta_p^2 = .13$, revealed faster response times for alcoholic ($M$ = 749 ms, $SD$ = 148) compared with nonalcoholic ($M$ = 801 ms, $SD$ = 207) original pictures, $t(33) = 5.13$, $p > .001$. There was no effect of stimulus type for scrambled or shape pictures ($p > .24$).

*Stimulus ratings*

There was no effect of stimulus type or group on picture recognition or arousal ratings. Valence ratings were affected by a stimulus type ×group interaction. For LD, there was a significant effect of stimulus type ($z = 3.01$, $p = .003$, heavy social drinkers: $z = 1.70$, $p = .089$). Alcoholic stimuli ($M$ = 0.4, $SD$ = 2.3) were rated more negatively then nonalcoholic stimuli ($M$ = 1.2, $SD$ = 1.8). Descriptive statistics can be found in Table 2.

#### *3.4.2 Questionnaires*

Handedness (EHI ratings) did not differ between groups, $t(31) = 0.84$, $p = .41$. There was no group effect on the IDTSA subscales "urges and temptations" and "pleasant time with others". Heavy social drinkers scored significantly higher on the subscales "pleasant/unpleasant emotions", "social pressure", "physical discomfort", and "conflict with others" (Table 1). PANAS revealed no significant effect of time on negative mood (all *p*s > .165). Positive mood scores were increased before ($M$ = 25, $SD$ = 6) compared with after ($M$ = 24, $SD$ = 7) the measurement, $F(1, 32) = 5.08$, $p = .031$, $\eta_p^2 = .14$. Nonparametric testing revealed no significant changes in alcohol craving across time and no difference between groups. Descriptive statistics are depicted in Table 2.

TABLE 2. State-dependent variables and ratings of the visual cues, $M$ ($SD$)

| Variable | HD | LD | Test statistics | *p* |
|---|---|---|---|---|
| PANAS | | | | |
| Pre-measurement negative mood | 11.3 (1.4) | 12.2 (2.6) | $t(23) = 1.26$ | .220 |
| Post-measurement negative mood | 10.6 (1.1) | 11.9 (2.4) | $t(19) = 1.89$ | .074 |
| Pre-measurement positive mood | 23.7 (5.7) | 26.4 (5.9) | $t(32) = 1.39$ | .173 |
| Post-measurement positive mood | 22.6 (6.6) | 24.6 (6.5) | $t(32) = 0.90$ | .377 |
| Pre-measurement craving (1–5) | 2.5 (1.8) | 2.1 (1.8) | $t(28) = 0.63$ | .537 |
| Post-measurement craving (1–5) | 2.2 (1.6) | 1.6 (1.2) | $t(27) = 1.05$ | .304 |
| Ratings on original pictures | | | | |
| Recognition alcohol (1–5) | 4.7 (0.3) | 4.5 (0.6) | $t(31) = 0.19$ | .854 |
| Recognition non-alcohol (1–5) | 4.5 (0.5) | 4.7 (0.4) | $t(31) = 0.80$ | .432 |
| Mean valence alcohol (-2 – 2) | 0.5 (2.5) | 0.3 (2.0) | $t(31) = 1.56$ | .129 |
| Mean valence non-alcohol (-2 – 2) | 1.2 (1.9) | 1.2 (1.7) | $t(31) = 0.05$ | .996 |
| Mean arousal alcohol (0–5) | 2.0 (1.2) | 1.7 (0.7) | $t(31) = 0.43$ | .670 |
| Mean arousal non-alcohol (0–5) | 1.8 (1.1) | 1.7 (0.8) | $t(31) = 0.72$ | .476 |

*Notes:* HD = heavy social drinkers; LD = light social drinkers; PANAS = Positive and Negative Affect Schedule.

*3.4.3 EEG data*

*P100 (amplitude and latency).* There was no significant P100 amplitude effect. In the content condition, there was a Stimulus × Group interaction on P100 latency, $F(1, 30) = 4.96$, $p = .034$, $\eta_p^2 = .14$. Latencies for alcoholic stimuli were shorter in HD ($M$ = 116 ms, $SD$ = 5) compared with LD ($M$ = 123 ms, $SD$ = 6). There was no main effect of group for nonalcoholic content (HD: $M$ = 123 ms, $SD$ = 6; LD: $M$ = 123 ms, $SD$ = 6). This interaction is shown in Figure 2.

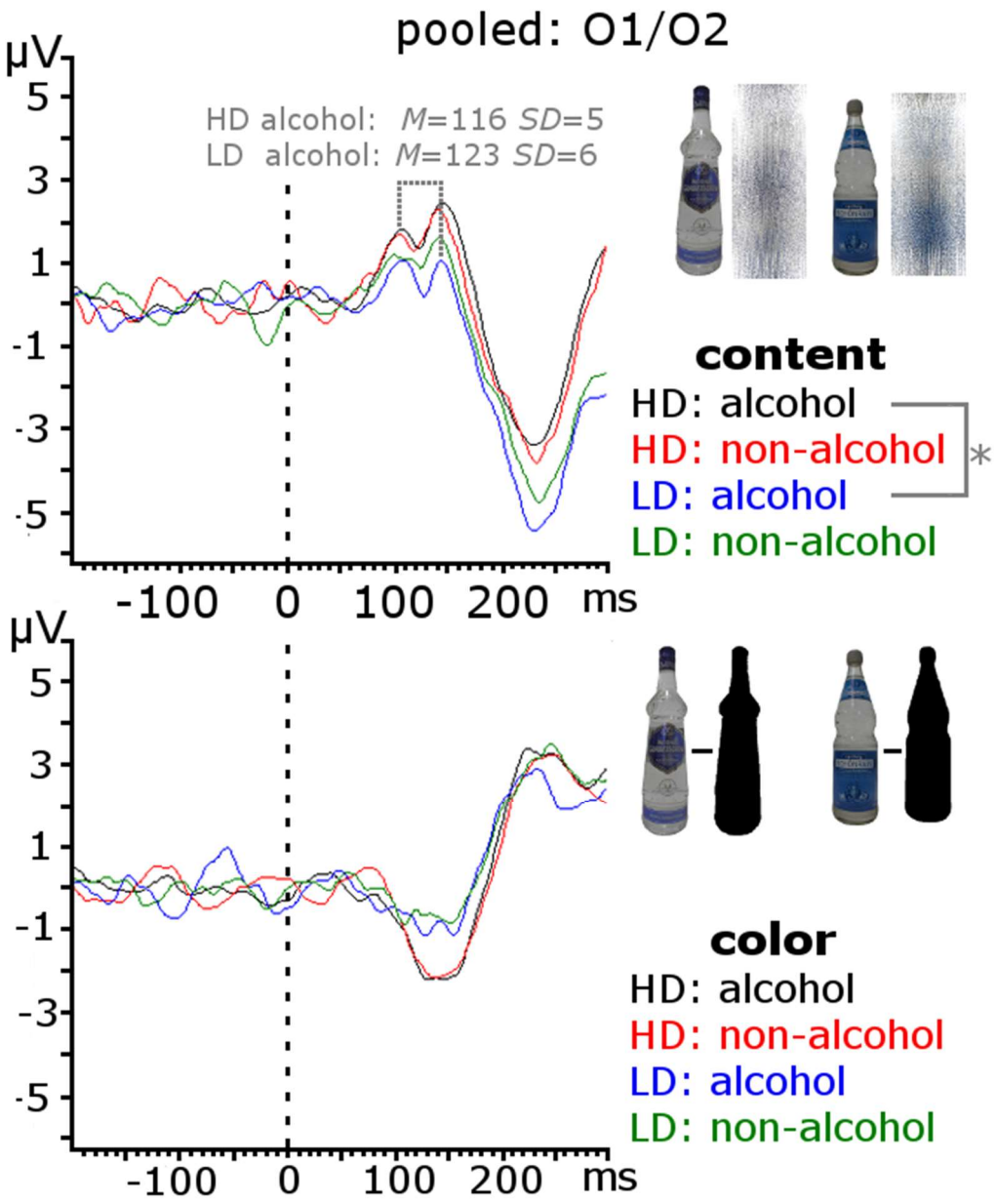


Figure 2 Difference waves at O1/O2 for content information (upper graph) and color-control condition (lower graph). Statistical analysis reveals shorter P100 latencies (ms) for alcoholic content in heavy social drinkers (HD) compared with light social drinkers (LD).

*LPP mean activity.* Content-related LPP mean activity (Figure 3a) revealed a significant Stimulus × Group interaction, $F(1, 30) = 4.59$, $p = .040$, $\eta_p^2 = .13$. There was a group effect related to alcohol content, $t(22) = 2.65$, $p = .015$. Alcoholic-cue LPP mean activity was increased in heavy social drinkers ($M = 2.52$ µV, $SD = 1.39$) compared with light social drinkers ($M = 1.55$ µV, $SD = 0.6$). No significant effect was found for visual-feature control LPP. See Figure 3 for difference waveforms and topographies for both the content (a–c) and the color control conditions (d–f).

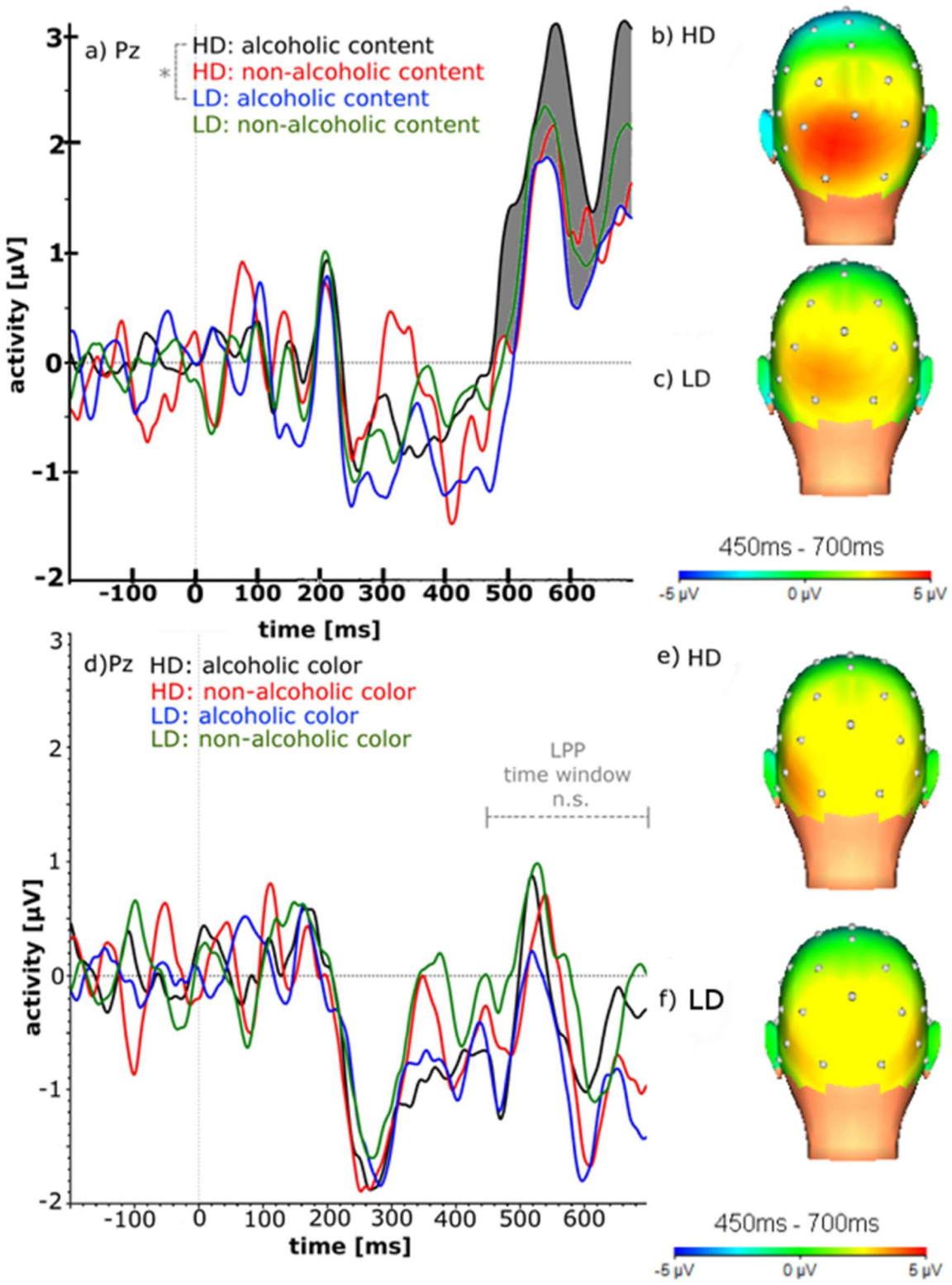


Figure 3 Difference waves at Pz for content information (upper graph) and color-control condition (lower graph). Statistical analysis reveals increased late positive potential (LPP) mean activity for alcoholic content for heavy social drinkers (HD) compared with light social drinkers (LD). Separate topographic distributions for heavy social drinkers (upper right) and light social drinkers (lower right) are depicted for both conditions.

*Regression.* In the alcohol content condition, regression of P100 latency and LPP on the AUDIT scores explained 24.8% of the variance, $F(2, 31) = 4.79$, $p = .016$. Model characteristics are depicted in Table 3. No regression in the other conditions yielded significance (all $F$s < 1). See Figure 4 for illustration.

TABLE 3. Regression statistics for each of the four models

| | | β | *T* | *p* |
|---|---|---|---|---|
| Alcohol content → AUDIT | | | | |
| | Constant | | 2.98 | .006 |
| | Latency P100 | -.354 | -2.11 | .043 |
| | Activity LPP | .464 | 2.76 | .010 |
| Alcohol color → AUDIT | | | | |
| | Constant | | 0.75 | .458 |
| | Latency P100 | -.004 | -0.02 | .984 |
| | Activity LPP | .089 | 0.46 | .649 |
| Non-alcohol content → AUDIT | | | | |
| | Constant | | 2.06 | .049 |
| | Latency P100 | -.137 | -0.73 | .469 |
| | Activity LPP | -.009 | -0.05 | .962 |
| Non-alcohol color → AUDIT | | | | |
| | Constant | | 1.86 | .073 |
| | Latency P100 | -.098 | -0.10 | .923 |
| | Activity LPP | -.544 | -0.54 | .590 |

*Notes:* AUDIT = Alcohol Use Disorders Identification Test; LPP = late positive potential.

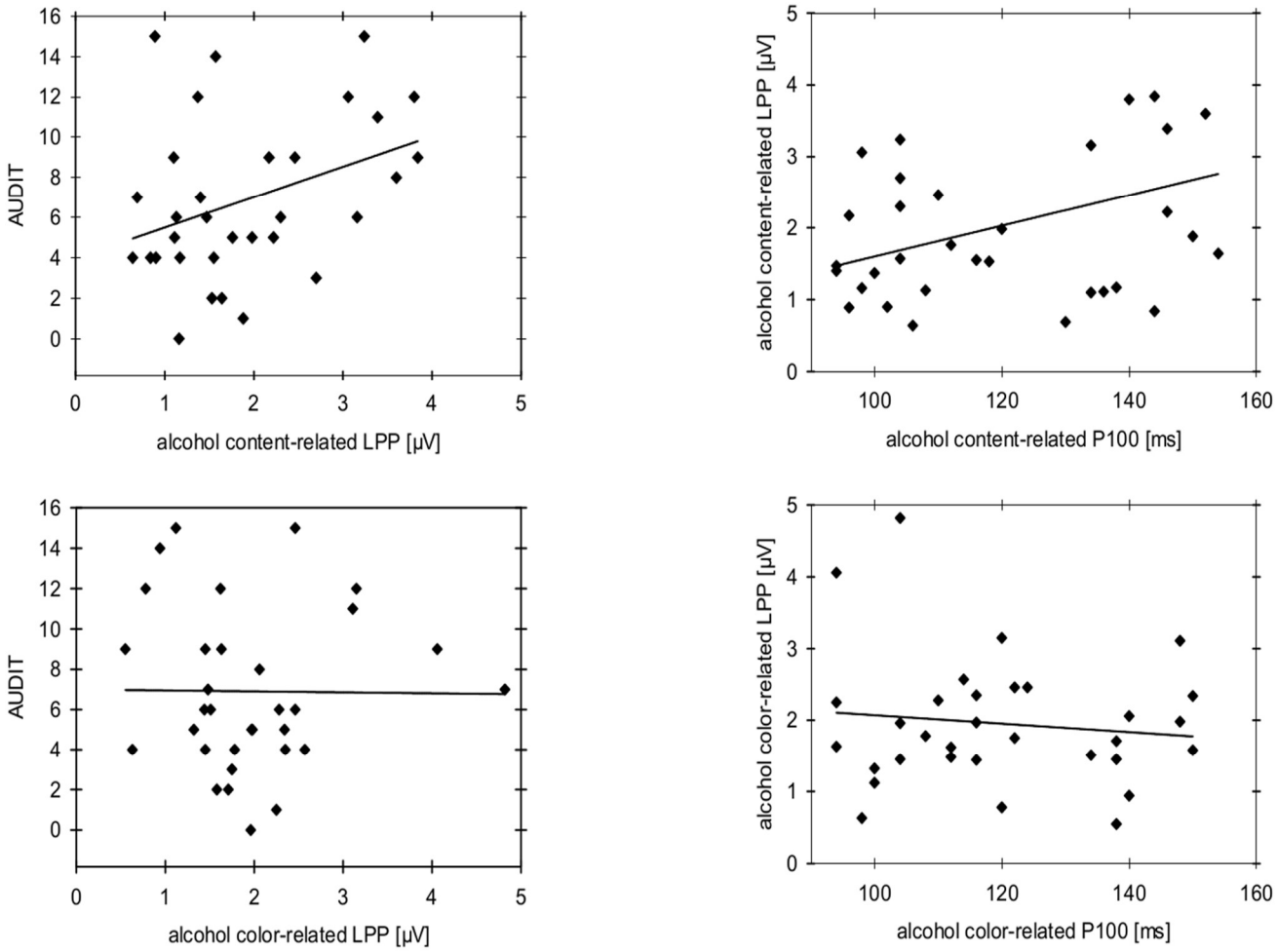


Figure 4 Scatterplot visualizing data included in the regression analysis. Correlation of late positive potential (LPP) alcoholic content difference waves (Pz) and Alcohol Use Disorders Identification Test (AUDIT) scores (upper left) and P100 latency with LPP activity (upper right). The lower diagrams depict the nonsignificant visual-feature-control condition.

### 3.5 Discussion

We analyzed cue reactivity during visual alcohol cue perception in a sample of HD not fulfilling ICD-10 criteria of alcohol dependency—and a control group with rare alcohol consumption (LD). Electrophysiological responses to visual beverage cues were investigated at both attentional (P100) and motivational (LPP) processing stages. Shorter P100 latencies (perception) and increased LPP mean activity (emotional valence) predicted hazardous alcohol use (assessed with AUDIT

scores) during the processing of visual alcoholic cues in the content condition (difference waves of original and scrambled pictures). This effect was not present in the visual feature control condition (difference waves of original and shape pictures). Both attentional and motivational processes were related to alcohol cue reactivity independent of visual features, e.g., color information, and will therefore be discussed in the following section.

The LPP reflects sustained attentional processing of motivationally significant stimuli (Matsuda & Nittono, 2015). In our HD sample, alcohol-related LPP was increased, indicating increased motivational significance. This result is in line with previous findings on increased LPP for cannabis (Wölfling et al., 2008), cigarettes (Minnix et al., 2013), and cocaine (Dunning et al., 2011) cues. To our knowledge, this is the first study to show an increased LPP in a HD sample and therefore needs further replication.

Furthermore, early alcohol cue-reactivity effects were reflected in shorter P100 latencies in HD. Latencies for visual evoked potentials were shortened for targets in an increased attention condition in healthy subjects (Di Russo & Spinelli, 1999). Compared with controls, latencies for neutral visually evoked potentials were prolonged in drug abusers (Garg et al., 2016). Such results are explained by increased motivational salience of alcoholic stimuli paired with simultaneous decreased salience of other stimuli in alcohol dependency (Volkow et al., 2009).

In our study, cue-reactivity measures predicted problematic alcohol drinking habits (AUDIT). Results indicated cue-reactivity effects on intensity and speed of stimulus processing in HD. These effects highlight timing issues as important factors in the design and analysis of cue-reactivity paradigms. Cue reactivity could be underestimated by the neglect of early brain response in HD, making time shifts important considerations when analyzing cue reactivity. Therefore, homogeneous analysis models for both addicted and healthy samples need to be critically revised. The functional meaning (less thorough perception vs. easier perception) of shortened latencies during alcoholic cue perception in HD needs to be further investigated. One shortcoming of the study was that cue reactivity was only assessed at an electrophysiological and biological level during the EEG measurement. Subjective craving ratings and other physiological measures of cue reactivity (HRV, skin-conductance response) could provide valuable additional information on different levels of cue reactivity.

Another methodological issue is the composition of the stimulus set used in the cue-reactivity paradigm. Beverages need to be familiar to the participants to enable reliable recognition and correct classification considering content (e.g., alcoholic vs. nonalcoholic). As we only considered correct classifications for the analysis, the power of the analysis depended on individual

beverage familiarity. We considered the familiarity effect by the computation of a variable we termed *representation strength* and added it to the model as a covariate. Our standardized stimulus set consisted of 20 different beverage pictures without individualization. Different beverage types (beer, wine, distilled spirits) were used independent of participants' preferences and drinking habits. This neglect of individual drinking preferences can underestimate cue reactivity. However, such individualization first required the analysis of impact of content information and visual features on cue reactivity performed in the current study.

To deduct content information, difference waves between recognizable beverages and their complementary nonrecognizable color equivalent were analyzed. Difference waves between correctly classified original and shape pictures were regarded as the visual feature control condition. Although physical properties are known to affect visual stimulus processing (Codispoti et al., 2012), there were no significant effects of the visual features of the beverage pictures on the cue-reactivity markers. Our results therefore indicate that highly standardized, visual feature–controlled stimulus sets are preferable to individualized stimulus sets when the goal is to increase cue-reactivity effects. Individual stimulus sets according to alcohol drinking habits, or an adaption of drink categories (beer, wine, distilled spirits), should be considered in further studies on alcohol cue reactivity.

Regarding subjective ratings of the depicted beverage pictures, there was no effect of stimulus type on valence or arousal in HD. Because ratings were averaged across the whole stimulus set (alcohol vs. nonalcohol, separately) equivalently to electrophysiological data, the impact of a high rating on single cues is averaged out. The study design and the analytic approach can therefore explain the lack of significant differentiation between alcohol and nonalcohol stimuli in HD on valence and arousal ratings. In LD, alcohol stimuli were rated more negatively in valence then nonalcohol stimuli. This is an expected result, as a positive affective response to alcohol stimuli is a function of personal experience (Pulido et al., 2009).

A further limitation of this study is the small sample size, requiring strong effect sizes to reach significance. Likewise, the extent of variables included in the analysis was limited. Variables such as smoking status and family history of SUD were not included here but have to be considered in further research to explain more variance in the sample. In our study, we relied on self-disclosure of psychiatric disorders. It remains of interest for follow-up studies to consider state markers for anxiety or depression to be able to quantify their relation to the investigated ERP.

Further studies could investigate the application of cue reactivity parameters. The applicability of cue-reactivity markers for the assignment to specific interventions and their prognostic value needs to be further investigated. Analyzing the electrophysiological basis (cue-

reactivity parameters) of interventions aimed at a modification of attentional or evaluative processes (e.g., mindfulness-based approaches) is highly relevant for a thorough understanding of their basic therapeutic mechanisms. A previous study using a mindfulness-oriented recovery enhancement was already able to find changes in LPP and markers of cue reactivity in an opioid misuse population of chronic pain patients (Garland et al., 2014).

Another intervention applied in relapse prevention in alcohol dependency is cue-exposure therapy. The intervention aims to change reinforcement contingencies of alcoholic stimuli by the exposure to one's preferred alcoholic drink without reinforcement through consumption (Mann & Brück, 2006). Effects of such interventions on cue-reactivity markers (P100 or LPP) need to be investigated. Furthermore, the current study raises the question of whether such findings could even be applied to predict the risk of a heavy social drinker to develop an alcohol dependency. Further research is also needed to investigate the predictive value of relapse in abstinent patients with alcohol dependency and the suitability of relapse as a marker for the assignment of therapeutic intervention.

## 4. Study2: Effects of Visual Alcoholic Cues on Error-Monitoring, Conflict Processing and Cognitive Control in Social Drinkers – A combined fNIRS-EEG study

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Kroczek, A. M., Haeussinger, F. B., Hudak, J., Fallgatter, A. J., & Ehlis, A.-C. (submitted). Effects of visual alcoholic cues on error-monitoring, conflict processing and cognitive control in social drinkers – a combined fNIRS-EEG study.

**4.1 Abstract**

Addictive behavior is characterized by fast automatic responses to drug-related cues (termed cue-reactivity) and insufficient cognitive control. There is evidence for cue-reactivity in heavy social drinkers (HD) as well. However, results on cognitive control are more ambiguous: error-monitoring, for instance, was found to be equal, reduced or augmented in HD compared to healthy controls. Here, we assessed cue-reactivity and error-monitoring interferences. Findings from error trials were related to subsequent error-adaptation. Functional near-infrared spectroscopy (fNIRS) spatial mappings of hemodynamic activity within the dorsolateral prefrontal cortex (dlPFC) were combined with temporally high-resolution electroencephalogram (EEG) measurements to resolve inconclusive findings from previous research.

60 German university students (n=30 HD and n=30 light social drinkers, LD) conducted a modified Eriksen Flanker Task cued by beverage pictures. Hemodynamic activity of the dlPFC was assessed (cognitive control) and related to error-monitoring (ERN/Ne) and post-error conflict monitoring (N2). Error-rates and post-error slowing (PES) were considered as behavioral measures.

Error-rates and PES did not differ between HD and LD. ERN/Ne amplitudes were reduced in HD during alcohol-cued trials and correlated with PES. In LD, post-error N2 amplitudes were increased and correlated negatively with ERN/Ne amplitudes. DlPFC activity increased after errors, independent of group or cue. In non-alcoholic trials, dlPFC activity furthermore correlated negatively with the number of errors in the same condition.

Error-monitoring is affected by alcohol cues in HD. This impairment is not reflected in general impairments on cognitive control. Instead, it seems that differences in the applied strategy for error-adaption indicate more efficiency in LD.

## 4.2 Introduction

### 4.2.1 A simplified model of addiction

Alcohol is very popular drug in our society, evidenced by its availability, legal advertisement and social acceptance. At the same time, alcohol has a large negative impact on societies with about 3.3 million deaths a year (5.9 % of all global deaths) attributable to alcohol consumption (WHO, 2015). In spite of its popularity, alcohol has clear addictive potential. Therefore, it is important to understand the transition from regular consumption to addiction to allow its reversal in addiction therapy. Addiction is characterized by an imbalance of automatized and deliberative behavioral regulation. In more detail, addictive behavior is guided by the automatized preference of the short-term benefits of drug consumption at the cost of deliberate consideration of serious negative outcomes, e.g., job loss or severe health problems (Bechara, 2002).

This aforementioned decision-making deficit is affected by an automatic conditioned response to alcohol-related cues (cue-reactivity), accompanied by insufficient response inhibition (cognitive control, Carter & Tiffany, 1999). The interplay of both systems in a HD sample at higher risk for transition to alcohol dependency is the focus of the current work. The automatic component contributing to decision-making deficits - cue-reactivity - is formed via mechanisms of classical conditioning through repeated pairing of immediate reinforcing alcohol effects to sensory alcohol-related cues and context cues (involving inner states). Cue-reactivity is manifested in subjective craving, physiological changes (e.g., increased sweating) or drug seeking behavior (Drummond, 2000).

Neurobiological correlates of cue-reactivity, revealed in fMRI studies, show increased activity within the ventral tegmental area, Ncl. accumbens, insula, amygdala, OFC and ACC in subjects with alcohol dependency (review: Jasinska et al., 2014). The functional meaning of these findings was interpreted within the model of enhanced salience, wherein sensitization of subcortical dopaminergic pathways to drug-related cues forms the biological background of cue-reactivity (Koob & Volkow, 2010). Furthermore, increased cue salience affects decision-making processes via this incentivized attentional bias (Jasinska et al., 2014). These findings were replicated in electrophysiological cue-reactivity markers even at a sub-pathological stage in HD (Herrmann et al., 2001; Petit et al., 2012a). Although HD are affected by cue-reactivity, their risk for transition to addiction is balanced. Potentially, intact cognitive control allows HD to compensate for cue-reactivity effects.

Cognitive control deficits are central to addiction. Besides the aforementioned overactive subcortical structures, decreased activity in the prefrontal cortex is related to cognitive control deficiencies (Crews & Boettiger, 2009). Cognitive control is fundamental for goal-directed behavior, as it allows deliberate adaptation of otherwise automatized behavior whenever abnormalities occur (e.g., alterations in contingencies). The ongoing monitoring of desired and perceived outcome allows the registration of such divergences as errors. Practically, intact cognitive control allows the inhibition of alcohol drinking when negative outcomes are perceived (problems at work, negative feedback from friends, health problems). Increases in cognitive control are found in HD (e.g. not drinking before exams) while severe deficiencies are found in alcohol dependency (e.g. drinking at work). Conclusively, the decrease in cognitive control is one feature of the progression from controlled drug use to dependency (Goldstein & Volkow, 2011). For a better understanding of the neurobiological background of this transition, error-monitoring and subsequent increases in cognitive control have to be considered.

### 4.2.2 Measuring error-processing

The Eriksen Flanker task is a convenient method to investigate error-monitoring. A correct response to the middle target stimulus (pointing direction of the middle arrow) despite flanking information (e.g. >><>>), requires inhibition of the flanking response. Response errors occur whenever flanking information is inhibited insufficiently, and are followed by the error-related negativity (ERN, Gehring et al., 1993)/error-negativity (Ne, Falkenstein et al., 1991), a fronto-central negative deflection generated within 100 ms after an erroneous motor response in the ACC (Carter & van Veen, 2007, Herrmann et al., 2004).

The reinforcement learning theory (Holroyd & Coles, 2002) explains the ERN/Ne by discrepancies between predicted and actual rewards signaled by the mesencephalic dopaminergic system via disinhibition of apical dendrites in the ACC. According to the conflict monitoring theory, on the other hand, the ERN/Ne is interpreted as a manifestation of high response conflict, signaling the need to augment cognitive control to the dlPFC, which allows for subsequent conflict reduction (Botvinick et al., 2001; Carter & van Veen, 2007).

The most consistent findings regarding addiction-related alterations in cognitive control are reduced ERN/Ne amplitudes and decreased dlPFC activity during inhibitory control in patients with SUD compared to controls; these findings, however, were not always linked to impaired task performance (for a review, see: Luijten et al., 2014). On the other hand, even increased ERN/Ne

amplitudes have also been reported in patients with alcohol-dependency (Padilla et al, 2011), especially with comorbid anxiety (Schellekens et al., 2010). These contradictory findings were interpreted in terms of compensatory resource allocations to achieve behavioral outcomes comparable to controls. However investigations on cognitive control in alcohol dependent subjects are confounded by the effects of chronic alcohol exposure on neurodegeneration in the prefrontal cortex (Chanraud et al., 2007). To focus on the functional interplay of cognitive control and cue-reactivity without this confounding factor, we focused on HD. Findings on cognitive control and error-monitoring in HD show either reduced ERN/Ne amplitudes (Smith & Mattick, 2013), or no difference in ERN/Ne amplitudes with increased error rates (Smith et al., 2017). On the other hand, an EEG study within our own lab revealed increased ERN/Ne-amplitudes in HD (Ehlis et al., submitted). To further clarify this ambiguous data, we measured cognitive control in addition to error-monitoring to capture potentially compensating mechanisms.

### 4.2.3 Measuring cognitive control and conflict-monitoring

The detection of response conflict and subsequent enhancement of cognitive control is known as the conflict-control loop (Carter & van Veen, 2007). During response conflict, increased cognitive control inhibits the response to a flanker stimulus during the subsequent trial (Larson & Clayson, 2011). As a major cortical player, the dlPFC is activated by increased response conflict and organizes cognitive control (e.g. Edwards et al., 2012; Gehring & Knight, 2000). Electrophysiologically, the conflict N2, a fronto-central negative peak occurring 250–350 ms after a stimulus, is elicited by competing response options like, for example, task-relevant vs. flanking information (Yeung & Cohen, 2006).

At the behavioral level, errors elicit an immediate slowing down of response times in the consecutive trial (post-error slowing, PES, Rabbitt, 1966), a well-described adaption to errors related to ACC activity (e.g. Danielmeier & Ullsperger, 2011). The ACC-generated N2 amplitude correlates with PES (Larson & Clayson, 2011) and also correlates with processing of task-irrelevant information (Larson & Clayson, 2011; Yeung & Cohen, 2006). Accordingly, increased ERN/Ne amplitudes and decreased N2 amplitudes are related to improved error-monitoring and response conflict reduction (Larson & Clayson, 2011). Hence, both an increased activation of the dlPFC and decreased N2 amplitudes can be considered adaptive processes to preceding error responses.

4.2.4 Hypotheses

To investigate interferences of cue-reactivity and cognitive control, we elicited cue-reactivity with visual alcohol-related cues precedent to an Eriksen Flanker task. We focused on the effects of alcohol cues on error-monitoring and cognitive control in HD. Analysis of error-monitoring (ERN/Ne) requires the high temporal resolution provided by EEG, while the assessment of cognitive control within the broad prefrontal cortex requires a good spatial resolution. Near-infrared spectroscopy (NIRS) is an optical method capturing cortical hemodynamics (concentration of oxygenated and deoxygenated hemoglobin) with good spatial resolution of the prefrontal cortex that, importantly, can be measured simultaneously with EEG. Accordingly, we were able to assess fast error-monitoring (EEG) and subsequent adaptions in the prefrontal cortex (dlPFC). We expected cue-reactivity effects in HD (stimulus-effect on ERN/Ne) and compensation by cognitive control related to comparable behavioral outcomes. Following reinforcement learning hypotheses, ERN/Ne amplitudes should be decreased during alcohol trials. However, our previous work revealed increased ERN/Ne amplitudes in HD, particularly during trials preceded by alcohol cues (Ehlis et al., submitted). This highlights the importance of the assessment of cognitive control (PFC activity) during such tasks to capture putative compensatory mechanisms. Therefore, a NIRS measurement of the dlPFC was conducted simultaneously to the measurement of ACC-generated ERPs (ERN/N2). To unravel compensatory processes, we analyzed adaptive mechanisms during errors and in trials thereafter.

## 4.3 Methods

*4.3.1 Participants*

66 healthy participants (age: 18-41; without current psychiatric, neurological or chronic internal diseases) were recruited. 6 subjects were discarded due to bad data quality, resulting in a final sample of 60 participants. The AUDIT (Saunders et al., 1993), was used for screening of drinking habits. Participants were categorized as LD or HD according to the total amount of consumed alcoholic drinks within the past 30 days, with equal distribution of sex (median split, cut-off female = 12, male = 32 standard drinks).

Group characteristics describing drinking behavior (Lindenmeyer & Florin, 1998) and significant differences on personality traits in impulsivity (BIS-11, Hartmann et al., 2011) and conscientiousness (NEO-FFI, Körner et al., 2002) are reported in Table 4. Alcohol dependency was excluded according to the ICD-10 criteria for alcohol dependency (World Health Organisation, 1992).

The study was approved by the Ethics Committee of the Faculty of Medicine at the University Hospital of Tuebingen and informed written consent was given by all participants.

**TABLE 4.** Questionnaire-based group-characteristics

| | HD | LD | Test statistics |
|---|---|---|---|
| Age (years) | 24 (±5) | 27(±6) | $t_{(58)}$ = 1.82, p = .072 |
| total drinks (last 30 days) | 45 (±22) | 8 (±9) | $t_{(38)}$ = 8.51, p < .001 |
| Drinking events in last 30 days | 12 (±4) | 5 (±5) | $t_{(58)}$ = 5.92, p < .001 |
| AUDIT score | 11 (±6) | 3 (±3) | $t_{(38)}$ = 6.83, p < .001 |
| unpleasant emotions [a] | 3.9 (±3.2) | 1.8 (±2.8) | $t_{(58)}$ = 2.61, p = .012 |
| physical discomfort [a] | 3.8 (±2.2) | 2.4 (±2.7) | $t_{(58)}$ = 2.14, p = .036 |
| conflict with others [a] | 2.1 (±2.6) | 0.6 (±1.6) | $t_{(58)}$ = 2.60, p = .012 |
| testing personal control [a] | 1.2 (±3.1) | 0.8 (±2.3) | $t_{(58)}$ = 0.54, p = .594 |
| pleasant emotions [a] | 17.2 (±12.8) | 9.0 (±6.9) | $t_{(58)}$ = 3.02, p = .004 |
| urges and temptations [a] | 6.1 (±4.0) | 3.4 (±4.2) | $t_{(58)}$ = 2.43, p = .018 |
| social pressure to use [a] | 12.4 (±5.6) | 10.7 (±7.6) | $t_{(58)}$ = 0.98, p = .333 |
| pleasant times with others [a] | 17.2 (±5.7) | 11.0 (±7.2) | $t_{(55)}$ = 3.80, p < .001 |
| Barratt Impulsiveness Scale-11 (BIS-11) | 62.4 (±7.0) | 56.4 (±8.2) | $t_{(58)}$ = 3.02, p = .004 |
| Conscientiousness (NEO-FFI) | 2.6 (±0.5) | 3.0 (±0.5) | $t_{(56)}$ = 2.77, p = .008 |

[a] IDTSA subscales

### 4.3.2 Modified Eriksen Flanker Task

Figure 5 depicts task parameters. Beverage pictures were validated in a different sample of HD/LD in a cue-reactivity ERP study (Kroczek et al., 2018). During the Eriksen Flanker Task (Eriksen & Eriksen, 1974), the hand for the correct response was determined by the symbol (arrow/triangle), while the correct response finger (index or middle finger) was determined by the tip of the middle

symbol (pointing either left or right). Subjects received visual feedback indicating correct ("+"), incorrect ("-"), or late ("!") responses. The cut-off for late responses was set by the median response time during 32 practice-trials. The experiment consisted of 400 trials, with breaks after every 100 trials.

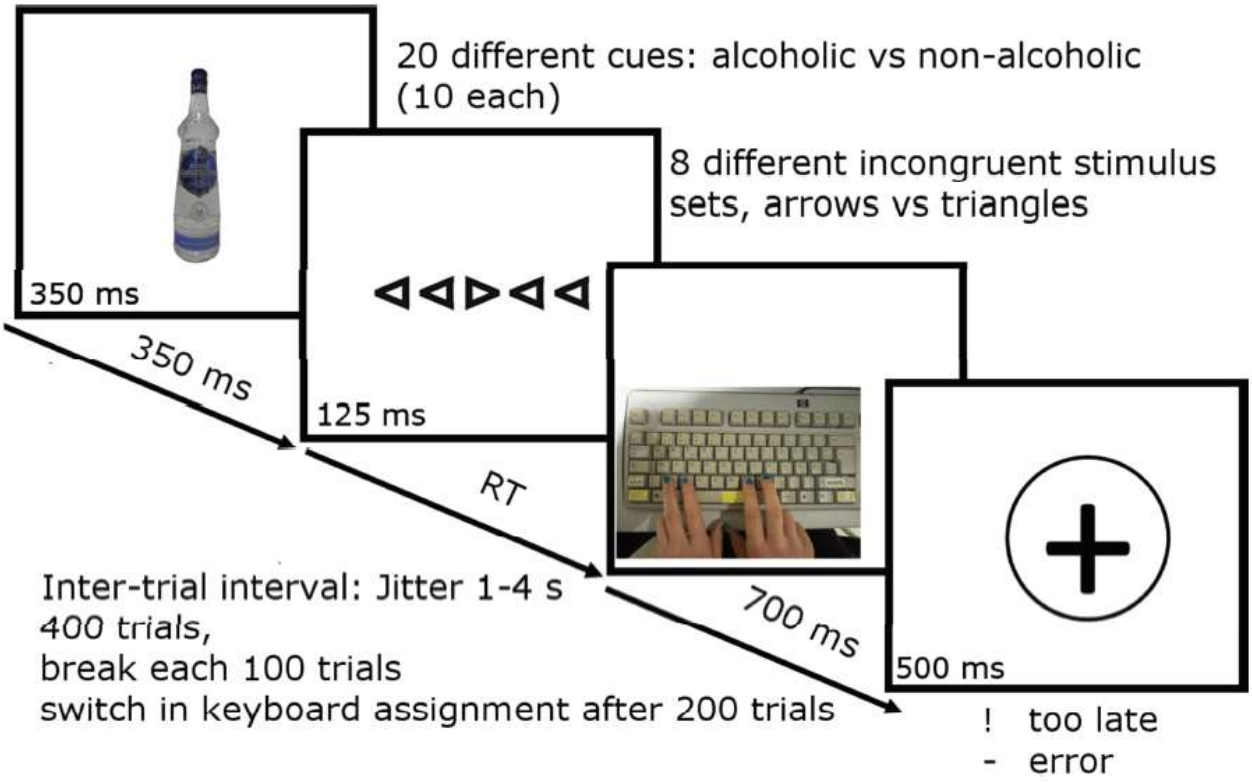


Figure 5 Task parameters for beverage cued Eriksen Flanker Task.

4.3.3 Electrophysiological recordings and analysis (EEG)

EEG was recorded using Ag/AgCl ring electrodes at 29 scalp sites according to the international 10-20 system (Jasper, 1958). FCz was used as recording reference and data were re-referenced offline to a common average. Two electrodes at the outer canthi of both eyes and an electrode beneath the right eye were applied to record eye movements. Data was recorded with a 1000 Hz sampling rate using a 0.1–100 Hz bandpass filter implemented in the Vision Recorder software (Brain Products, Munich). All impedance values were kept at ≤5kΩ. Data was analyzed using the BrainVision Analyzer software (Brain Products, Munich). After a 40 Hz low-pass filter, an independent component analysis was applied to correct ocular and muscle artefacts.

*4.3.3.1 Error-related negativity (ERN/Ne)*

For response-locked analyses, baseline-corrected segments (from 200 ms before the motor response to 700 ms thereafter) were extracted (baseline period: -200 to -50 ms), separately for correct and error responses following alcoholic vs. non-alcoholic cues. Finally, four ERP curves were averaged for every participant (each 6 segments minimum, Olvet & Hajcak., 2009). Amplitudes and latencies at FCz (determined as the most negative peak in the time-window: -30 ms to 150 ms) were individually analyzed.

*4.3.3.2 Conflict monitoring (N2)*

For stimulus-locked analyses, baseline-corrected segments (from 200 ms before the motor response to 700 ms thereafter) were extracted (baseline period: -200 to 0 ms), separately for trials with alcoholic vs. non-alcoholic cues following either correct or incorrect previous trials. Finally, four ERP curves were averaged for every participant (each 20 segments minimum). Amplitudes and latencies at FCz (most negative peak in time-window: 150–300 ms) were individually analyzed.

**4.3.4 Recordings of blood oxygenation level dependent (BOLD) responses and analysis (fNIRS)**

The ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) was used with a 3×15 optode holder on both hemispheres (30 mm inter-optode distance) incorporated into an EasyCap with EEG electrodes at fronto-temporal sites (cf. supplementary material for the placement of the 2×22 NIRS-channels and their anatomical labels) oriented towards FCz and Cz. Analysis was based on self-written Matlab scripts (The MathWorks Inc., Natick, USA). Preprocessing consisted of visual inspection and bandpass filtering (0.01-0.5 Hz). Correlation-based signal improvement was used for the correction of motion artifacts (Cui et al., 2010). Brain activation was inferred in a model-based approach with condition (error vs. hit / post-error vs. post-hit) and cue (alcoholic, non-alcoholic) as regressors, convolved with a γ-hemodynamic reponse function (HRF from SPM8, peak at 6 s). The $\beta$-values were calculated by means of least-square linear regression including a first-order autoregressive model (Plichta et al., 2007).

Four ROIs within the prefrontal cortex were analyzed, averaging the respective channel $\beta$-values: left BA46 (CH9, CH13, CH17) and BA9 (CH17, CH21, CH22) and right BA46 (CH5, CH14) and BA9 (CH19, CH20). Anatomical labels were assigned in an independent sample (n=6) using neuronavigation of the applied probe-set to individual anatomical MRI pictures.

### 4.3.5 Statistical Analysis

Statistical analysis was conducted with IBM SPSS Statistics 21. Repeated measurement ANOVAs were used for ERN/Ne amplitudes/latencies and hemodynamic responses during error trials with response (correct vs. error) and cue (alcoholic vs. non-alcoholic) as within-subject factors and group as between-subject factor. Correspondingly, N2 and adaptive hemodynamic responses were analyzed in a previous-trial (post-hit vs post-error) and cue (alcoholic vs non-alcoholic) repeated-measurement ANOVA.

Only the highest-level interactions involving cue, response or group are reported; Greenhouse-Geisser correction was used whenever necessary. Normal distribution of the data was tested by Kolmogorov-Smirnov tests. Non-parametric testing was used for variables deviating from normal distribution. ERP amplitudes were correlated (Pearson's r) with *β*-values, error-rates and PES separately for both groups and with respect to cue-type.

## 4.4 Results

4.4.1 Behavioral data (error-number, response time and PES)

Error rates did not differ between groups, neither on alcoholic ($\chi^2$=0.51, $p$=0.48) nor non-alcoholic ($\chi^2$=0.74; $p$=.39) trials. Error rates in HD were independent of cue ($Z$=1.58, $p$=0.12), whereas error rates were decreased in LD after alcoholic cues (Z=2.03; $p$=0.04). Reaction time was independent of cue or response (all F<1). The preceding response affected reaction times on correct trials ($F_{(1,56)}$=98.75; $p$<.001; $\eta^2$=.638), with Longer reaction times for post-error ($M$=422 ms; $SD$=85) compared to post-hit trials ($M$=388 ms; $SD$=85), which is described as PES.

4.4.2 EEG data

*4.4.2.1 ERN/Ne.* Response type affected ERN/Ne latency ($F_{(1, 56)}$=14.42, $p$<0.001, $\eta^2$=.21), with prolonged latencies on error compared to correct trials (cf. Fig. 6). A cue × group interaction ($F_{(1, 56)}$=7.52, $p$=0.008, $\eta^2$=.12) revealed a stimulus effect in HD ($t_{29}$= 2.96 ; $p$=.006), but not in LD ($t_{29}$=0.55 ; $p$=.59), indicating prolonged latencies in alcohol-cued trials compared to non-alcohol-cued trials.

ERN/Ne amplitude was affected by condition ($F_{(1, 56)}$=98.98, $p$<0.001, $\eta^2$=.64) with increased amplitudes during error trials ($M$=-3.57 µV, $SD$=2.22) compared to hits ($M$=-1.04 µV, $SD$=2.20). The stimulus × condition × group interaction ($F_{(1, 56)}$=4.22, $p$=0.045, $\eta^2$=.07) revealed a stimulus ×

condition interaction in HD ($F_{(1, 28)}$=11.34, $p$=0.002, $\eta^2$=.29), but not LD ($F_{(1, 28)}$=0.33, $p$=0.570, $\eta^2$=.01). In HD, ERN/Ne amplitudes were decreased ($t_{29}$=3.98; $p$<.001) after alcoholic ($M$=-2.59 µV, $SD$=3.22) compared to non-alcoholic cues ($M$=-4.55 µV, $SD$=2.). There was no significance for correct trials (alcohol: $M$=-.86 µV, $SD$=2.83, non-alcohol: $M$=-.97 µV, $SD$=2.74; $t_{29}$=0.61; $p$=.54).

In trials with non-alcoholic cues, ERN/Ne amplitudes and error numbers correlated in HD ($r$=.523, $p$=.003) and LD ($r$=.478, $p$=.008). Alcohol-cued ERN/Ne amplitude correlated with PES in HD ($r$=.399, $p$=.029), and LD ($r$=.403, $p$=.027).

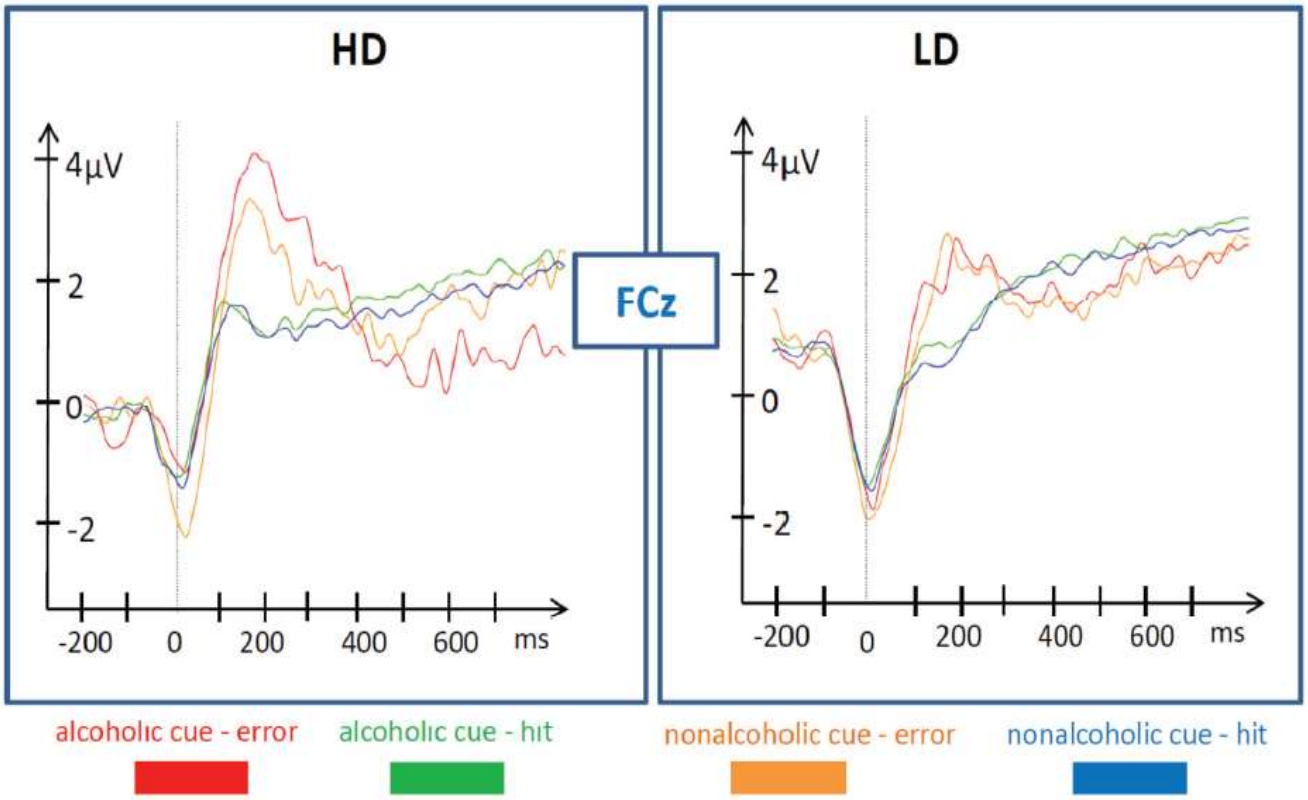


Figure 6 ERN/Ne amplitudes at FCz in HD (left) and LD (right), separately for cue (alcoholic vs. non-alcoholic) and response types (hit vs. error).

*4.4.2.2 Post-error N2*

There was no N2 latency effect. The pre-response × group interaction on N2 amplitudes ($F_{(1, 58)}$=6.31, $p$=.015, $\eta^2$=.098) revealed an effect of previous-trial in LD ($F_{(1, 29)}$=21.82, $p$<.001 $\eta^2$=.429), with higher amplitudes for post-error ($M$=0.67 µV, $SD$=3.0) compared to post-hit trials ($M$=1.8 µV, $SD$=2.4). There was no significance in HD ($F_{(1, 29)}$=3.61, $p$=.067 $\eta^2$=.111). In LD, alcohol-cued ERN/Ne amplitude correlated with post-error ($r$=-.362, $p$=.049) and post-hit N2 ($r$=-.378, p=.040).

### 4.4.3 NIRS data

*4.4.3.1 Response on error trials*

Response type affected every ROI (cf. Fig. 7 for *β*-values, Tab. 5 for statistics), revealing decreased *β*-values during errors. In rBA9, the cue × response interaction revealed a more prominent decrease during error trials following non-alcoholic (vs alcoholic) cues (cf. Fig 8).

**TABLE 5.** Statistics for ROI analysis

| ANOVA effect | | statistics |
|---|---|---|
| Response | lBA9: | $F_{(1, 58)}$= 46.84, $p$<.001, $\eta^2$= .46 |
| | rBA9: | $F_{(1, 58)}$= 33.33, $p$<.001, $\eta^2$= .37 |
| | lBA46: | $F_{(1, 58)}$= 10.60, p=.002, $\eta^2$= .16 |
| | rBA46: | $F_{(1, 58)}$= 7.60, p=.008, $\eta^2$= .12 |
| | | $F_{(1, 58)}$= 6.55, $p$=.013, $\eta^2$ = .10 |
| cue | Alcohol-hit vs alcohol-error: | $t_{59}$= 4.24; $p$<.001 |
| × | Non-hit vs non-error: | $t_{29}$= 5.27; $p$<.001 |
| response | Alcohol error vs non-error: | $t_{29}$= 1.05; $p$=.298 |
| | Alcohol hit vs non-hit: | $t_{29}$= -1.47; $p$=.147 |

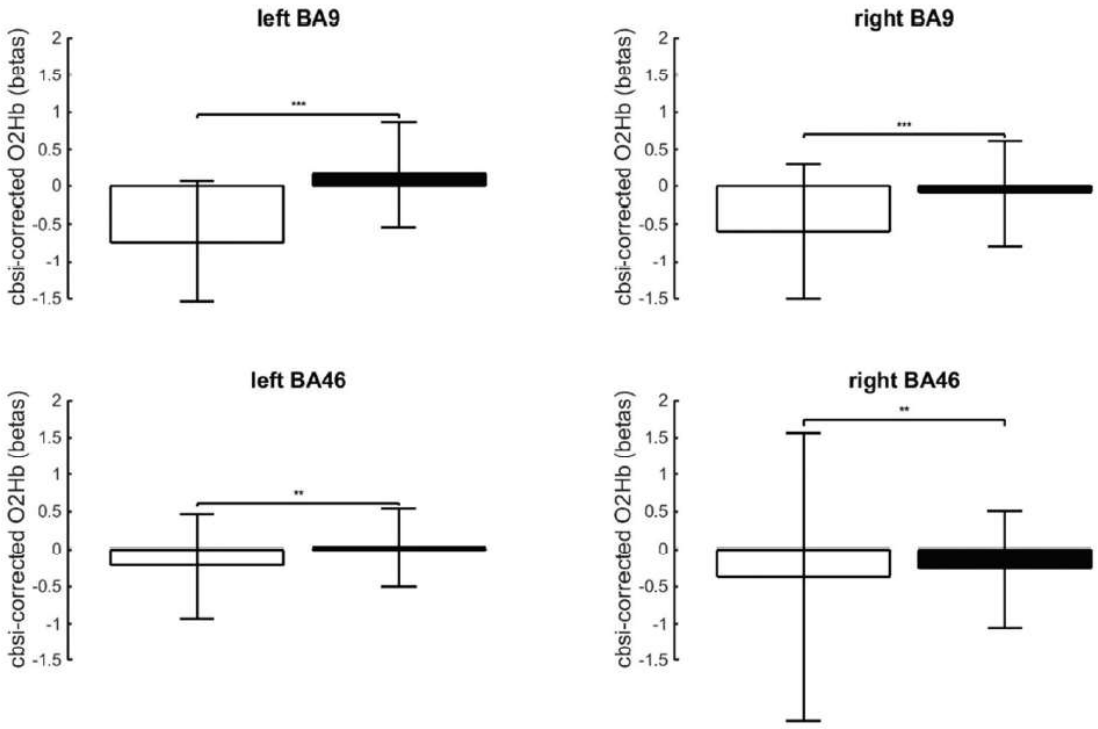


Figure 7 *M (SD)* of *β*-values for cbsi-corrected $O_2Hb$ in 4 ROIs: white bars indicate error trials, black bars show correct trials. Standard deviations of means are depicted for each bar.

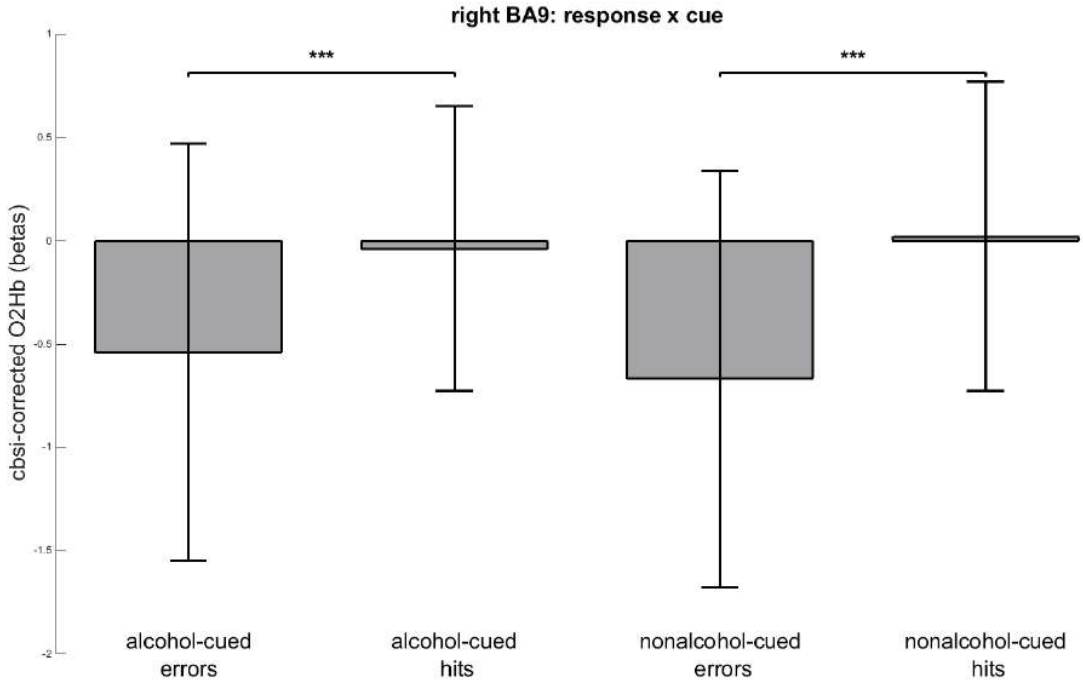


Figure 8 *M (SD)* of *β*-values for cbsi-corrected $O_2Hb$ right BA9. Standard deviations of means are depicted for each bar. Significant differences are indexed via asterisk: ***= *p*<.001

*4.4.3.2 Post-error dlPFC activity*

Preceding responses (correct vs. incorrect) affected activity in the left [BA46: $F_{(1, 58)}$=9.07, $p$=.004, $\eta^2$=.14; BA9: $F_{(1, 58)}$=4.20, $p$=.045, $\eta^2$=.07] and right [BA46: $F_{(1, 58)}$=10.67, $p$=.002, $\eta^2$=.16; BA9: $F_{(1, 58)}$=6.70, $p$=.012, $\eta^2$=.10] dlPFC on the current trial. There was an overall post-error increase in hemodynamic responses compared to post-hit activity in the dlPFC (Fig. 9).

During non-alcohol trials, activity in the right dlPFC on post-hit trials correlated with error-number in HD ($r$=-.369, $p$=.045). In LD, error-number correlated with non-alcoholic post-hit lBA9 ($r$=-.665, p<.001) and lBA46 (r=-.640, p<.001) activity. Furthermore, non-alcoholic ERN/Ne amplitude correlated with post-hit activity in rBA9 ($r$=-.427 $p$=.019) and rBA46 ($r$=-.466, $p$=.009). In HD, post-error activity in lBA9 correlated with error-number in non-alcoholic trials ($r$=-.435, $p$=.016), while post-hit dlPFC activity correlated with alcohol-cued PES ($r$=-.412, $p$=.024).

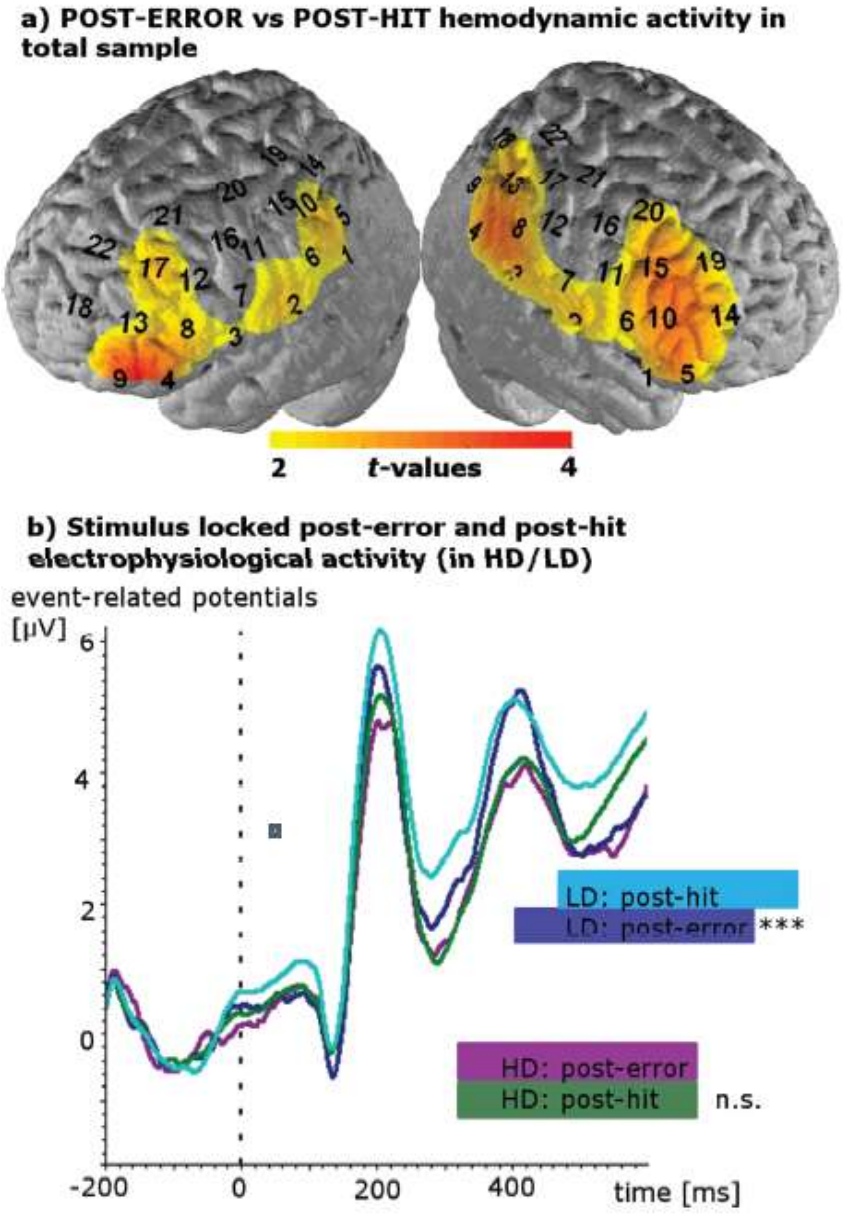


Figure 9 Adaptive processes in a) hemodynamics, *t*-values of post-error vs. post-hit contrast mapped onto the brain b) Stimulus-locked (Flanker-Task) N2, separately for HD and LD with respect to response in previous trial

### 4.5 Discussion

Within this study, the effects of alcoholic cues on error-processing (ERN/Ne), cognitive control (hemodynamic activity in dlPFC) and adaptive effects on the following trial were analyzed in HD and LD. Cue-reactivity effects on error-processing were confirmed for HD: ERN/Ne amplitude was reduced in alcohol-cued trials. Furthermore, alcohol-cues delayed ERN/Ne latencies in HD. There were no overall differences at the behavioral level (response times, PES, error number) between groups. Interestingly, a cue-effect appeared in terms of reduced error rates in LD in alcohol-cued trials. N2 amplitude was modulated by the response (correct vs. error) in the previous trial in LD independent of cue, with increased amplitudes following errors. Similarly, in the dlPFC, activity was increased after errors compared to post-hit trials. While ERN/Ne amplitudes correlated with N2 amplitudes in LD, they correlated with PES during alcohol-cued trials in HD. In non-alcohol

cued trials, relations were more straightforward: ERN/Ne amplitudes correlated with error rates in both HD and LD.

Reduced ERN/Ne amplitudes in HD during alcohol-cued trials are in line with earlier studies showing, e.g., decreased ERN/Ne amplitudes during smoking cue-exposure in smokers (Luijten et al., 2011). This ERN/Ne amplitude effect is in line with the reinforcement learning theory (Holroyd & Coles, 2002): as no reinforcement occurs despite alcoholic cues, the outcome is worse than expected, inducing reduced activity in ACC, which possibly interferes with error-monitoring. Additionally, errors (ERN/Ne), latencies were prolonged ERN/Ne latencies in HD supports the theory of interference with cue-reactivity networks.

This main result is contrary to a previous finding with a similar paradigm (Ehlis et al., submitted), where alcohol-cued ERN/Ne amplitudes were increased in HD. One explanation for the contradictory results are the characteristics of the study populations: While Ehlis et al. did not find differences on personality traits typical for HD, the current HD sample displayed increased impulsivity and decreased conscientiousness scores. A further difference between both studies is the increased trial length used here for methodological reasons (hemodynamic responses require longer inter-trial intervals). In future studies, those parameters need to be considered to capture a holistic view on cue-reactivity effects on error-monitoring.

Still, reduced ERN/Ne amplitudes in alcohol-cued trials in HD did not affect the behavioral level (comparable to the behavioral data in the study of Ehlis et al.) suggesting compensatory mechanisms. Moreover, an increased post-error PFC activity was observed in both groups, independent of the cue condition. This finding is in line with the conflict monitoring theory, which suggests that ACC activity in high-conflict situations acts as a trigger for subsequent increases in cognitive control. Evidently, even the reduced ERN/Ne amplitudes in HD triggered an increase in cognitive control comparable to LD. A general group difference, however, was found for stimulus-related conflict processing in terms of reduced N2 amplitudes after correct responses compared to errors only in LD. In contrast, HD did not show any differentiation in conflict processing depending on the response outcome of the previous trial. Increased N2 amplitudes were previously related to higher response conflict during stimulus perception (Folstein & Van Petten, 2008) and discussed as an index of conflict magnitude, suggesting more efficient conflict processing with reduced N2 amplitudes (Larson et al., 2014). We therefore conclude that reduced N2 amplitudes after correct responses in LD reflect more efficient conflict monitoring. Furthermore, the ERN/Ne was negatively correlated with N2 amplitudes in LD, implying that more intense error-processing was followed by reduced conflict-processing on the following trial. These data indicate more efficiency in error

monitoring and cognitive control in LD compared to HD. This is especially relevant when cognitive control is considered a limited resource as in the model of "ego depletion" (Baumeister, 2003). The effect of inefficient cognitive control in HD beyond the measurement should be further considered, e.g. in terms of measures for behavioral inhibition, to further investigate this assumption.

During our measurement, however, there was no group effect on behavioral measures. Shortened PES in subjects with alcohol (Lawrence et al., 2009), cocaine (Ide et al., 2016) and opioid (Liao et al., 2014) dependency could not be found in HD. This is in line with a previous study of Ehlis et al. (submitted). We found a correlation of attenuated alcohol-cued ERN/Ne amplitudes with prolonged PES in HD replicating previous findings of decreased ERN/Ne amplitudes with prolonged PES (Gehring et al., 1993). However, a reversed relationship has also been reported in healthy subjects (Cebrian et al., 2016). A possible interpretation for these inconsistencies in PES findings is the use of additional adaptive mechanisms aimed at reducing the probability of an error by decreasing response conflict, such as post-error reduction of interference (PERI). There is evidence that PES and PERI rely on different cortical activation and deactivation patterns (King et al., 2010) and seem to constitute largely independent post-error adjustments (Danielmeier & Ullsperger 2011). The assumption of inter-individual variance regarding the use of such strategies is supported by our results, as ERN/Ne amplitudes correlating negatively with N2 amplitudes in LD reflects PERI.

There is evidence for an unspecific slowing down of responses after errors in HD, opposed to a more specific reduction in conflict monitoring in LD, indicating different underlying processes of error compensation. In HD, alcohol-cued PES was shorter when dlPFC activity was higher throughout the experiment. For trials preceded by non-alcohol cues, on the other hand, post-error dlPFC activity determined error-number. In HD, cue-type modulated error-compensation via a general increase in response times after errors (PES) rather then a decrease of response conflict (PERI).

Interestingly, LD showed lower error rates on alcohol-cue trials, while HD were not affected by cue-type. The beverage pictures used in this study were previously validated in a different sample of HD and LD, revealing more negative valence ratings of alcohol stimuli in LD (Kroczek et al., 2018). Therefore, a possible interpretation is that alcoholic cues were processed like stimuli with negative value in LD. There is evidence for shorter reaction times and higher accuracy during trials with a negative stimulus during a face-word stroop task (Yang et al., 2016). Results were interpreted as increased priority of negative stimuli was interpreted as processing priority effect of negative stimuli. Lower error rates in alcohol-cued trials in LD can thus be interpreted as a valence effect.

An overall effect in the whole sample was broad dlPFC deactivation on error trials, probably preceding the occurrence of an error. We did not lock our analysis to the time window before error commission which is necessary to confirm this hypothesis and should be considered in future studies.

Our data highlights that a combination of fNIRS and EEG is a convenient method to capture error-monitoring and subsequent adjustments in cognitive control. Multimodal measurements increase validity, which is especially important to unravel complex processes. Our data supports basic assumptions of the reinforcement-learning theory (considering ERN/Ne modulation by alcohol cues) as well as the conflict-monitoring hypothesis of a causal relation of ACC and (subsequent) dlPFC activation. A combined model should be further considered in future studies.

Limitations

Our main finding, reduced ERN/Ne amplitudes in HD after alcohol cues, contrasts with previous findings from of our group reporting increased ERN/Ne amplitudes in HD (Ehlis et al., submitted). A possible explanation is the difference in personality characteristics between the samples that are known to affect action monitoring potentials, such as conscientiousness and impulsivity (e.g. Pailing and Segalowitz, 2004). This is a general problem in this investigation field, as there might be a systematic difference between HD and LD in those characteristics that may be difficult to disentangle from more specific alterations in action-monitoring.

Furthermore, timing is a problem inherent in measurements of the hemodynamic response. As the hemodynamic response occurs within seconds after an event, we could not distinguish whether we captured a dlPFC response to the initial error or the visual external feedback the subjects received, or even a deactivation preceding the occurrence of the stimuli. In order to disentangle processes of error monitoring and feedback processing – or, more precisely, events leading up to error -- analysis strategies have to be refined to gain more information from multimodal imaging and overcome such shortcomings.

Future directions

Impairments in cognitive control were shown to predict smoking relapse better then cue-reactivity markers (Luijten et al., 2016). Markers assessing effects of cue-reactivity on cognitive control could even increase the predictive value and should therefore be investigated in patients with substance use disorders in relation to clinical outcome parameters, e.g. relapse intensity. We did not assess subjects with alcohol dependency in our study. It would be intriguing, however, to

verify the hypothesis of an additional lack of cognitive control in dependent subjects in the presence of alcoholic cues compared to HD.

For the improvement of analysis methods in multimodal measurements, there is a trend towards single trial analyses (Huster et al., 2012). The analysis of single trials seems to be more informative then averaged responses, especially in the analysis of errors, which are rare events. Our study revealed that simultaneous fNIRS-EEG measurements are a convenient method to analyze cue-reactivity interference with error-processing. Still, analytical approaches should be extended to exploit the full potential of multimodal measurements.

## 5. Study 3: Prefrontal Functional Connectivity measured with Near-Infrared Spectroscopy during Smoking Cue Exposure

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Kroczek, A. M., Haeussinger, F. B., Fallgatter, A. J., Batra, A., & Ehlis, A.-C. (2017). Prefrontal functional connectivity measured with near-infrared spectroscopy during smoking cue exposure. *Addict Biol, 22(2),* 513-22.

## 5.1 Abstract

Cue-Reactivity is an important concept for relapse in SUD. Although cue exposure therapy is discussed as relapse prevention, current approaches still need improvement considering its efficacy. From a neurobiological perspective, cue-reactivity is related to an over-activation in sensitized subcortical structures, their projections to motivationally relevant cortical structures (e.g. OFC) and deficient prefrontal inhibitory control. Therefore, we analyzed prefrontal cortical activation and its relation to craving during smoking cue exposure. We focused on the OFC – as a projection area of sensitized subcortical structures – due its importance in the processing of reinforcement value and the dlPFC based on its importance for behavioral inhibition. fNIRS was used to assess hemodynamics in prefrontal regions during smoking cue exposure in 24 subjects ($n$ = 12 occasional smokers, $n$ = 12 controls). Subjective craving intensity (minimum craving as marker of baseline inhibition, range as marker of inhibition time course) was additionally assessed. Craving ratings indicated that cue-reactivity was elicited solely in smokers, not controls. Those subjective ratings correlated with hemodynamic activity in OFC (craving range) and dlPFC (minimum craving). OFC activation was found earlier throughout the cue exposure in smokers compared to controls. Connectivity (seed-based correlation) between OFC and dlPFC was increased in smokers. fNIRS can capture prefrontal hemodynamic activity involved in cue-reactivity elicited during cue exposure and is therefore a promising method to investigate cue-reactivity and its implications for relapse prevention in SUD.

## 5.2 Introduction

One major feature of SUD is the high risk of relapse related to persistent addiction memory. Operant conditioning is thought to be the mechanism by which addiction memory may evolve into the manifestation of a SUD (Drummond, 2000). Positive short-term effects of a drug of abuse lead to increased consumption and can evolve to addiction, which is in turn associated with co-occuring perceptions by means of the reinforcing values of the drug of abuse, relying on principles of classical conditioning (Garbusow et al., 2014). Addiction memory can be triggered by drug related cues, e.g. the sight, smell, mood and context related to drug consumption (Carter & Tiffany, 1999). Formerly neutral stimuli are able to elicit

reactions preparing drug consumption hence becoming a discriminative cue for the activation of the addiction network.

The active addiction memory expresses itself as a conditioned response referred to as cue-reactivity. One aspect of this cue-reactivity is the subjective perception of a strong urge to consume a drug of abuse described as craving (Carter & Tiffany, 1999). Alcohol craving is a predictor of relapse in detoxified alcoholics (Heinz et al., 2009) and, likewise, there appears to be a predictive value of craving on tobacco relapse (Berlin et al., 2013). As conditioning principles are highly related to the evolvement of addiction memory, it is plausible to consider the involvement of extinction processes in its reversal (Everitt, 2014).

Extinction learning is induced by repeated presentation of a conditioned stimulus, e.g. drug related cues uncoupled from its reinforcing features (unconditioned stimulus), i.e. drug consumption in the case of SUD. The behavioral effect of extinction is supposed to be a reduction of the intensity and frequency of a conditioned reaction. In SUD, the cue-reactivity expresses itself as craving at a subjective level and overt drug-seeking behavior. From a biological perspective, there is evidence that extinction learning is related to an increase in inhibitory connections from prefrontal to subcortical areas rather than erasing old conditioned stimulus-associations (Everitt, 2014). Cue-reactivity in addiction is highly related to sensitized, overactive subcortical regions (David et al., 2005; Vollstadt-Klein et al., 2012; Wrase et al., 2002) like the VTA and the nucleus accumbens (review: Schacht et al., 2013). Regulating cue reactivity, however, is related to activation in cortical regions such as the dlPFC (Kober et al., 2010). During drug cue exposure, insufficient inhibitory control of regions like the dlPFC co-occurs with subcortical over-activation related to compulsive, non-planned drug-seeking behaviors.

A consistent finding in SUD samples compared to controls is hypoactivation in the ACC, the inferior frontal gyrus and the dlPFC (Luijten et al., 2014). These neural activation patterns probably constitute a major problem in addictive behavior possibly expressed at the behavioral level as lack of inhibitory control over impulsive choices or actions.

The dlPFC is related to extinction learning (Delgado et al., 2008) through connections to the OFC which has subcortical efferences from neuronal structures involved in addiction memory. Considering principles of extinction learning, repeated cue exposure without the immediate reinforcing effects of a substance of abuse increases dlPFC activation. Translated to a clinical perspective this should be reflected in lower craving and relapse in SUD. This is

the basic principle of cue exposure therapy (CET, Conklin & Tiffany, 2002). The aim of CET is to experience craving to decrease without consumption. CET was investigated in patients with alcohol (Mann & Hermann, 2010), nicotine (Unrod et al., 2013) cocaine (O'Brien et al., 1990) and heroin (Du et al., 2014) dependency. A meta-analysis on cue-reactivity reveals that results are inconsistent (Conklin & Tiffany, 2002). A better understanding and improvement of CET is therefore necessary.

In the current study, we will explore activation and functional connectivity of the aforementioned cortical structures during smoking cue exposure in smokers compared to subjects without addictive memory related to cigarettes. Considering extinction learning and habituation as basic principles involved in CET, we expect changes in cortical activation in the course of cue exposure in brain regions involved in cue-reactivity (OFC) and regions involved in behavioral inhibition (dlPFC) in smokers. As we consider the dysregulated connectivity of the described neural structures a major problem in SUD, there will be a strong focus on connectivity between those regions involved in addiction memory that are on the outer cortical layer and therefore accessible with fNIRS. fNIRS is a neuroimaging method steadily gaining traction in psychiatric research (Ehlis et al., 2014). For investigations of cue-reactivity there are several benefits in using fNIRS, e.g. subjects are sitting in a realistic upright position and can handle real objects to elicit cue-reactivity by triggering several senses (visual, tactile, olfactory, and interoception during movement). Although fNIRS cannot measure hemodynamic activity in subcortical structures, it can assess both the dlPFC involved in inhibitory processes and the OFC involved in the processing of emotional valence.

We focus on a comparison of occasional smokers and controls. In contrast to controls, occasional smokers were shown to depict cue-reactivity comparable to subjects with nicotine addiction (Carpenter et al., 2013). Suitability of fNIRS to capture cue-reactivity and functional connectivity during CET will be evaluated. Considering the basic mechanisms of CET, we expect to find more activity in the OFC and the dlPFC. Ideally, we expect to find an evolvement of subjective craving and its decrease throughout the cue exposure session in smokers. This expected pattern relies on the aforementioned condition principles as well as habitation processes and constitutes the CET rational.

## 5.3 Methods

### *5.3.1 Participants*

A total of 28 subjects (aged 20-31 years) were recruited to take part in the experiment. Exclusion criteria were any neurological/chronic internal diseases or any history of psychiatric disorders (according to the DSM-IV screening questionnaire), besides nicotine dependence. Each subject of the smoking sample (n = 14) reported having smoking events within the past 30 days (assessed with timeline-follow back method, Sobell et al., 2003). According to the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991), 12 subjects revealed a light consumption pattern (FTND 0-2), whereas 2 subjects had scores indicating modest (FTND=6) or heavy nicotine dependence (FTND = 8). Hours since the last smoked cigarette ranged from 0.5 to 240 (*M* = 42.0, *SD* = 70.2) in smokers. Control subjects (n = 14) had smoked less then 10 cigarettes during their lifetime.

A total of 4 subjects (2 smokers and 2 controls) had to be excluded from the final sample due to heavy artifacts (technically evoked superimposed sinus waves or fast, steep oscillation exceeding 0.5 mm*mmol/l) in the NIRS data resulting in a final sample of 12 smokers and 12 controls. Gender was equally distributed across groups (female: 8, male: 4 in both the smoker and control sample). Mean values and statistics for subscales of the Barratt Impulsivity Scale (Hartmann et al., 2011) are shown in Table 1. All participants had normal or corrected-to-normal vision and took part on a voluntary basis with the offer to receive course credit. The study was approved by the Ethics Committee of the Faculty of Medicine at the University Hospital of Tuebingen and all procedures were in accordance with the Declaration of Helsinki in its latest version. Informed written consent was obtained for all participants after receiving instructions and a detailed explanation of the study.

Table 6 Age and characteristics of both the smoking and control sample according to Barratt Impulsivity Scale scores for each of its three scales. Mean (SD) values and statistics are shown.

| | Smoker (n = 12) | Controls (n = 12) | Statistics |
|---|---|---|---|
| Age (years) | 25 (3) | 24 (1) | $t_{22}$ = .95, p = .325 |
| Nonplanning Impulsiveness | 19 (4) | 17 (2) | $t_{18}$ = 2.0, $p$ = .065 |
| Motor Impulsiveness | 20 (5) | 16 (3) | $t_{17}$ = 2.3, $p$ = .033 |
| Attentional Impulsiveness | 27 (3) | 23 (2) | $t_{18}$ = 3.0, $p$ = .008 |

*5.3.2 fNIRS*

fNIRS data was acquired with the ETG-4000 Optical Topography System (Hitachi Medical Cooperation, Tokyo, Japan). NIRS optodes were mounted in a plastic holder with 3 rows of 11 optodes and a fixed interoptode distance of 3 cm. This probeset was fastened above the forehead with the middle optode of the lowest row above Fpz and the outer optodes on both sides above T3 and T4 respectively (according to the 10-20 system, Jasper, 1958). MNI positions for each of the 52 NIRS channels were assigned based on anatomic MRI scans of 4 volunteers (head circumferences of 54 cm and 56 cm, respectively) wearing the NIRS probeset during a neuronavigation session using the LOCALITE TMS Navigator (Biomedical Visualization System, Sankt Augustin, Germany). Measured coordinates were normalized using SPM8 and individual structural MRI scans. Mean variability of the individual coordinates of the four subjects to the calculated mean coordinates used for anatomical assignment was 7.44 mm. The mean of those normalized coordinates was subsequently used to estimate the most probable underlying Brodman area for each channel. This assignment, and the alignment of the probeset according to the 10-20 system, are visualized in Figure 10.

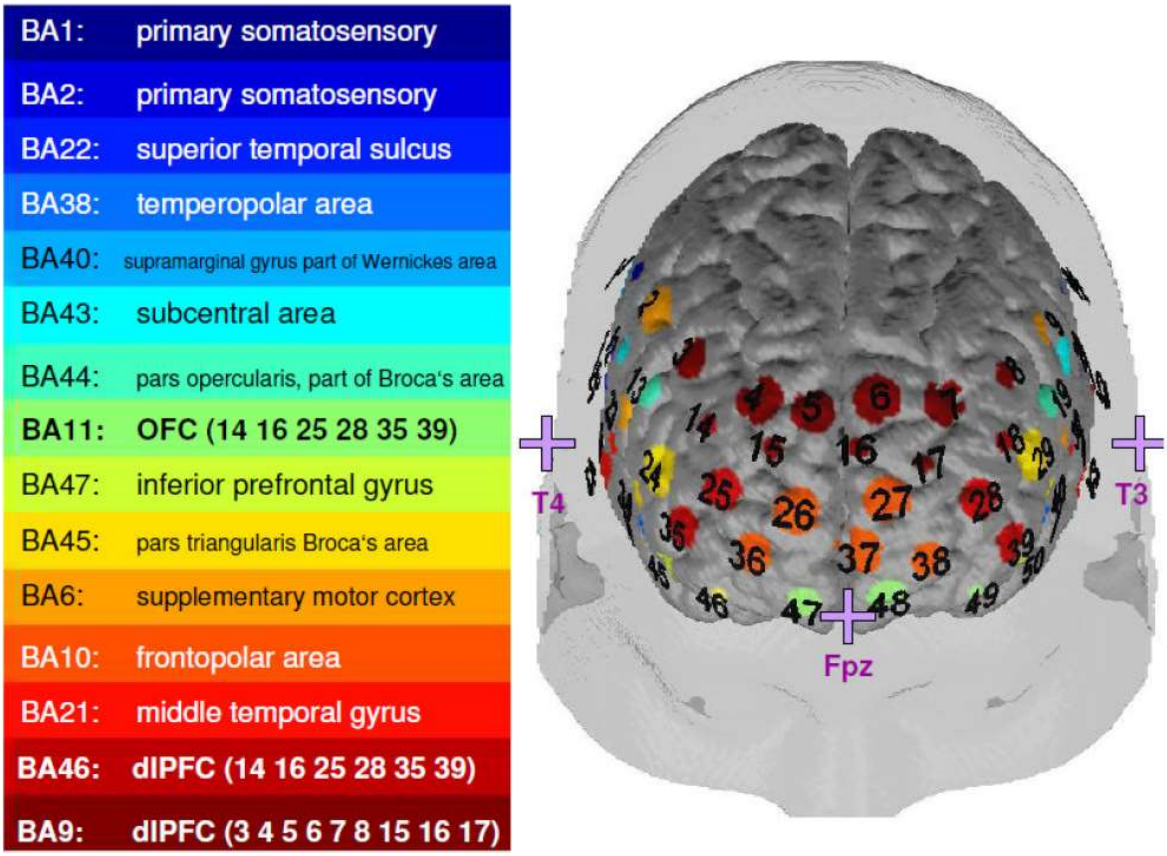


Figure 10 All Brodman areas measured by the applied probeset of fNIRS optodes are represented and visualized on the brain surface. Regions of Interest (dlPFC, OFC) are characterized by involving the exact channel numbers applied for analysis. Additionally head model is marked by violet crosses indicating the orientation points for the placement of the fNIRS optode holder.

*5.3.3 Procedure*

After giving informed consent, participants filled out the questionnaires (demographic data, FTND, Timeline-Followback Calender). After mounting the NIRS optode probset as described above, subjects performed a modified color-word Stroop Task (Stroop, 1935) intermixed with the presentation of pictures with negative valence, smoking cues or neutral pictures. Results of this task will be described elsewhere. The following *in vivo* CE was instructed by an audiotaped male voice triggered by Presentation software (Version 14.5, www.neurobs.com). Total duration this smoking cue exposure was 15 minutes.

First, subjects were informed about the procedure. Subjects were asked to give a verbal rating, regarding their current craving, on a scale from 0 to 10, where 0 represents no urge and 10 represents a very strong urge to smoke a cigarette. This subjective craving was assessed one minute after each new instruction. Cue exposure instructions gradually

increased in intensity adapted from a therapeutic intervention related to alcohol dependence (Mann et al., 2006) and will be further described subsequently. After each instruction, subjects had 1 minute to concentrate on the cues before being asked about their current craving. At first, subjects were instructed to imagine a situation in which they experienced a strong urge to smoke a cigarette ("imagination" task). After assessing the craving, the examiner put a tray on the table in front of the subject containing a pack of cigarettes, tobacco, filters, cigarette leaves, a lighter and an ashtray. Subjects were instructed to visually examine the contents of the tray ("vision" task). After that, there was a tactile stimulation ("touch" task) followed by an olfactory stimulation ("smell" task). Then subjects were instructed to use the lighter and to perform smoking movements including the contact of the cigarette with the mouth ("move" task). Then subjects were encouraged to increase craving by doing whatever they preferred with the exception of lighting the cigarette. Subjects were asked to roll a cigarette if they wanted to ("roll" task). Thereafter, the instruction to pay attention to changes in craving, bodily sensations or thoughts was given ("relax" task).

*5.3.4 Preprocessing of fNIRS data*

To correct for movement and physiological artifacts, a bandpass filter (0.01 – 0.5 Hz) was applied to the raw NIRS signal. This was the only preprocessing step applied for the analysis of functional connectivity. The prefrontal region is prone to fNIRS signal distortion by *extra-cranial* blood flow regulated by sympathetic activity (Kirilina et al., 2012). We assume that these distortions play a critical role in this study, because the used paradigm is designed to induce craving that is likely connected to sympathetic activity. Therefore deoxygenated hemoglobin (HHb) was considered for analysis, as it is less affected by skin-blood flow, as shown by Heinzel et al. (2013) and Haeussinger et al. (2014). For analyzing time courses of activation changes, mean levels of HHb were additionally separated into 60 sec bins for a total of 15 minutes of cue exposure. Whenever concentration differences between adjacent bins exceeded 0.1 mm*mmol/l, this was considered a mechanical artifact and a spline interpolation was conducted for the respective outlier bin using self-programmed scripts. Time course during instruction and craving rating periods were kept in the analyzed bins, as subjects often started the task during instruction and kept on going during ratings. Assignment of bins to the respective task (including instruction and ratings) are shown in Fig.11.

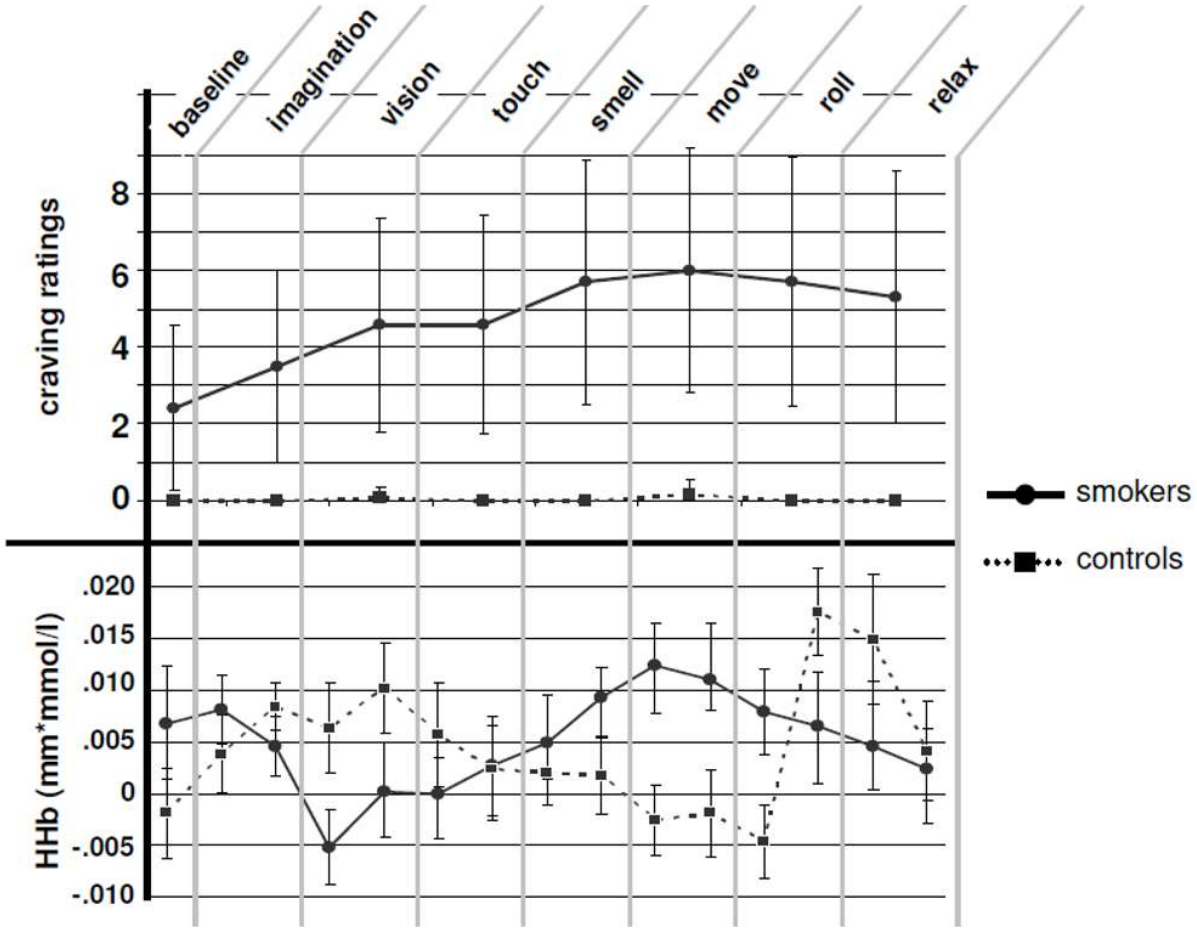


Figure 11 In the upper part, craving rations (0-10) with respect to the according CE task are shown, below time course of OFC HHb concentration (mean values for CH47, CH48, Ch49) is depicted. Each dot represents the mean value for a 1 minute bin during the cigarette CE.

*5.3.5 Statistics*

For the time course of smoking cue exposure, the statistical analysis was conducted separately for the mean values of channels related to our regions of interests as earlier definied: BA11 (CH47, CH48, CH49) and dlPFC subdivided further into left BA9 (CH6, CH7, CH17), left BA46 (CH18, CH28, CH39), right BA9 (CH3, CH4, CH5, CH15, CH16) and right BA46 (CH14, CH25, CH35). A repeated measurement ANOVA was run for each ROI separately. Whenever the sphericity assumption was not met, the Huynh-Feldt correction was applied. Further testing of significant interactions was conducted with Student's t-test.

For the connectivity analysis, the time series for a seed channel was correlated (Pearson correlation) with each time series of the remaining 51 channels (seed-based correlation analysis). Choosing a seed-ROI instead of a representative seed-channel yielded similar results,

yet channel wise-analysis was more clear-cut. For reasons of conciseness, we only report the channel-based analysis within pre-defined ROIs. We chose CH18 out of our left dlPFC ROI, as it is an approximation for F3, CH47 was extracted from the right OFC ROI as seed, for its approximation to Fp2 (according to 10-20 system). Those equivalents of 10-20 positions were chosen as they represent a common standard montage for stimulation of the left dlPFC (Nitsche & Paulus, 2007) which is discussed as the stimulation site for treatment of craving (Jansen et al., 2013). Therefore, we chose channels equivalent to F3 (CH18) and Fp2 (CH47) as seed regions in order to assess usual activation and connectivity patterns during cue exposure before further investigating their modulation by neurostimulation (in a future study).

For both seed-based correlation analyses, a randomization test was performed to test for statistical significance. The idea of this bootstrap approach was to evaluate whether the found connectivity in a given ROI (BA9, BA46 or OFC) is high compared to the remaining non-ROI channels. Therefore, we calculated the probability (p-value) to find a ROI of randomly assigned channels that features a higher connectivity then the original ROI. We consider the found ROI connectivity as significant if the ratio of randomly assigned ROIs with a higher connectivity is lower than 0.05. We started the randomization test by creating a group map of connectivity. To this end, we calculated t-values for each channel by performing one-sample t-tests using the Fisher transformed correlation coefficients. Consecutively, we determined a reference ROI t-value, i.e. ROI connectivity, by summing up the t-values for all channels that belonged to a ROI (BA9, BA46, OFC). This reference ROI t-value was compared to 5000 other ROI t-values that were identically calculated for 5000 random rearrangements of channels. The resulting p-value is the number of runs for which the reference ROI t-value was smaller than the random ROI t-value divided by the total number of runs. In the end, there is only one test for significance for each ROI (to test if the reference ROI t-value differs significantly from 5000 random t-values), overcoming the need to correct for multiple testing.

Additionally, we conducted nonparametric correlations of changes in subjective craving (range of expressed craving from 0-10) data, minimum craving rating (lowest craving rating), maximum craving rating (highest craving rating) and changes in HHb (summed up over time) of our predefined ROIs (OFC, BA9 and BA46 for both hemispheres). Minimum craving was chosen as marker for baseline inhibition, maximum craving was a marker of craving intensity, whereas craving range involved information about changes within the cue exposure time course. We predict craving ratings to evolve in a reversed u-shaped manner throughout the

cue exposure, therefore we used measures of craving describing its shape rather then a single value.

## 5.4 Results

### *5.4.1 fNIRS time course during smoking cue expsure (HHb)*

There was a significant time × group interaction regarding HHb concentration changes in the OFC ($F_{6,138}$ = 2.20, $p$ = 0.04, $\eta 2$ = .091). Post-hoc testing revealed significant group effects in the mean activity during the "vision" task ($t_{22}$ = 2.02, $p$ = .05), "motion" task ($t_{22}$ = 2.77, p = .01) and "roll" task ($t_{22}$ = 2.3 $p$ = 0.3). Descriptive Statistics for the fNIRS time course during smoking cue exposure are depicted in Figure 11. Decrease in HHb concentration is part of a normal hemodynamic response (resulting from an increased oxygen supply to activated brain areas) and therefore reflects activation. Notably, the time effect differs between groups: smokers show a decrease in HHb concentration earlier ("vision" task) then controls ("roll" task). There was no significant effect of time or group in the other ROI.

### *5.4.2 Subjective ratings and their physiological correlates*

Controls had no significant changes in subjective craving over time (2 subjects rated craving with 1 once during smoking cue exposure, besides that, only zeros were recorded). Each smoker however reported craving at least once during the cue exposure (Minimum Craving: $M$ = 2.25, $SD$ = 2.18; Maximum Craving $M$ = 6.42 ; $SD$ = 3.12). Intra-individual changes in craving ratings ranged from 1 to 7 ($M$ = 4.17, $SD$ = 1.99). We found correlations (see Figure 12) of the individual craving range and HHb concentration changes in the OFC ($r_s$ = -.601, $p$ = .039). Minimum craving correlated with HHb of left BA46 ($r_s$ =.614, $p$ = .034). We found no significant correlation of right BA46 or BA9 on both hemispheres with subjective craving ratings (r < .505, p > .095).

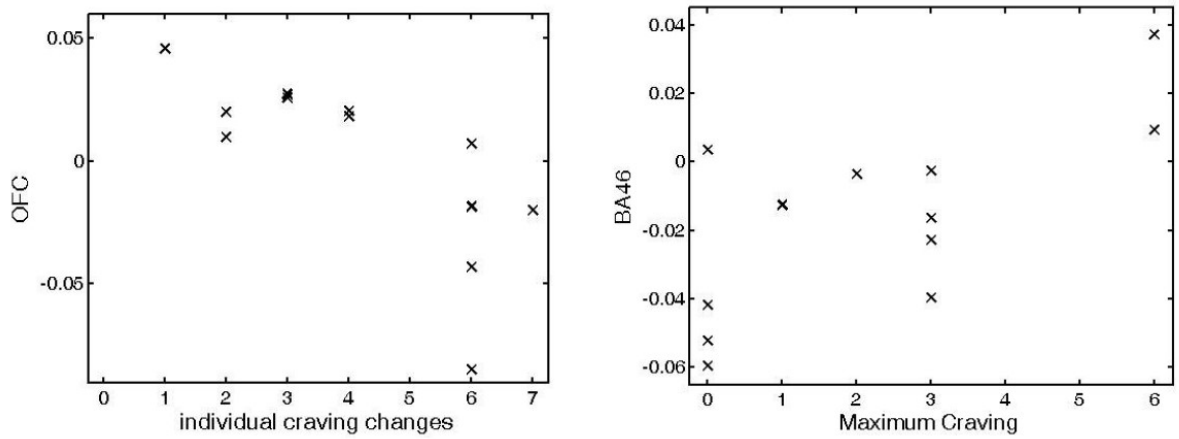


Figure 12 Correlations between subjective craving and changes in HHb during smoking cue exposure. On the left the correlation between OFC activity and changes in craving ratings is depicted. On the right, the relation of activity in the left BA46 and the minimum craving rating during the cue exposure is shown.

### *5.4.3 Seed-based correlation analysis during smoking cue exposure*

Analyzing the seed-based correlations revealed significantly higher connectivity of CH18 (left dlPFC) to the right BA9 ($p$ = .01) in smokers compared to controls (Figure 13a). Connectivity for CH47 with BA9 was higher for smokers compared to controls, $p$ = .0082 (Figure 13b).

In an additional, exploratory analysis, we regarded the connectivity during specific (sub-) tasks of the cue exposure. The uncorrected $p$-values for group effects for connectivity of dlPFC (CH18) to our ROI are reported in Table 7. We found significant group effects for connectivity to the contralateral dlPFC (BA9 and BA46) for different subtasks. As depicted in Table 8 for BA11 as seed (CH47), we found a significant group effect on connectivity to the right BA46 specifically for the “smell” instruction with increased connectivity in smokers. Interestingly, this segment directly preceded the “motion” condition where significant group differences were found for OFC activation (see above).

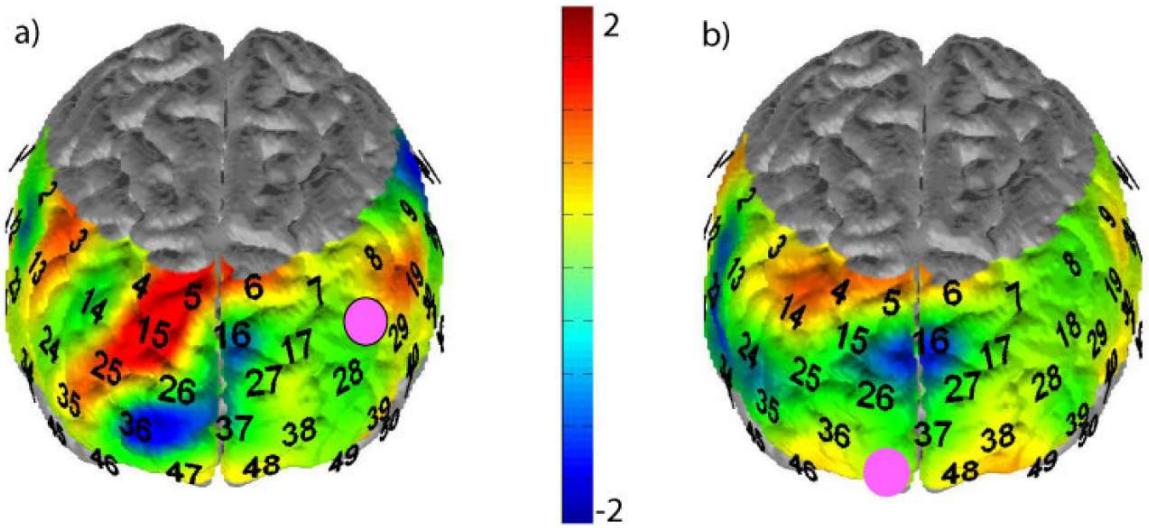


Figure 13 T-values for group differences between smokers and controls for seed-based correlations. The pink dot indicates the seed of the correlation a) Correlation seed is CH18 (left dlPFC), connectivity to the right dlPFC and the OFC is stronger in smokers compared to controls. b) Correlation seed is CH47, connectivity to the right dlPFC is stronger in smokers compared to controls.

Table 7 *The results of the randomization tests are shown as p-values for group differences (smokers vs. controls) in connectivity of seed CH18 to our ROI. Left BA46 is not included, as it is the seed region of CH18.*

| **Seed CH#18** | lBA9 | rBA9 | rBA46 | BA11 |
|---|---|---|---|---|
| Baseline | .35 | .16 | **.015*** | .93 |
| Imagination | .26 | **.018*** | **.016*** | .78 |
| Vision | .20 | **.0034*** | .68 | .68 |
| Touch | .26 | .50 | .19 | .70 |
| Smell | .051 | .17 | .061 | .32 |
| Move | .62 | **.0002***** | .11 | .80 |
| Roll | .38 | .10 | .56 | .17 |
| Relax | .73 | .51 | .56 | .90 |

Table 8 *The results of the randomization tests are shown as p-values for group differences (smokers vs. controls) in connectivity of seed CH47 to our ROI. Left BA11 is not included, as it is the seed region of CH47.*

| **Seed CH#47** | lBA9 | rBA9 | lBA46 | rBA46 |
|---|---|---|---|---|
| Baseline | .91 | .48 | .64 | .30 |
| Imagination | .44 | .87 | .75 | .46 |
| Vision | .88 | .82 | .70 | .88 |
| Touch | .16 | .21 | .18 | .62 |
| Smell | .37 | .061 | .17 | **.036*** |
| Move | .90 | .79 | .80 | .65 |
| Roll | .88 | .97 | .18 | .44 |
| Relax | .47 | .43 | .74 | .25 |

### 5.5 Discussion

Changes in craving during the smoking cue exposure confirm that the applied *in vivo* confrontation with smoking paraphernalia elicited cue-reactivity in smokers but not in controls. For fNIRS data, we did not find a main effect of group, but we did find differences in the timing of activation within the OFC. In detail, we found OFC activation in smokers at first sight of smoking paraphernalia. Controls, however, depicted OFC activation later, when instructed to increase their craving. This timing effect in OFC activation supports the notion that experiencing craving or imagining an intense value of a stimulus is not unique to regular smokers. It might simply be triggered more easily in this group, e.g. by already the sight of a stimulus. Regarding the other levels of cue-reactivity, we found a relation between physiological and subjective measures in smokers: a higher range in craving ratings was correlated with more activity in the OFC measured by means of HHb concentration decrease. This indicates that more activity in the OFC is related to subjective feelings of craving and their changes. Activity in the left dlPFC (BA46), however, was reduced in subjects reporting higher minimum craving. The more activation in the left dlPFC the lower was the baseline craving we found. This can be interpreted in terms of an inhibitory influence of dlPFC activation on the

intensity of perceived craving. These results indicate the utility of prefrontal fNIRS to capture cortical processes involved in cue-reactivity.

Additionally, the results of the seed-based correlation analysis support the utility of fNIRS as a convenient method for the analysis of prefrontal cortical networks. We found higher connectivity between left and right dlPFC in the smoking group. A possible interpretation is an increased effort for smokers to inhibit behavior that requires increased synchronization of both hemispheres. This effect could be shown for a motor task with increased complexity of the movement related to increased connectivity between the hemispheres (Rissman et al., 2004). Furthermore, we found differences in connectivity of the OFC and dlPFC between smokers and controls. Specifically, more simultaneous activity of the OFC and dlPFC was detected in smokers, probably reflecting the need of inhibitory activation when cue-reactivity is elicited for smokers only. For controls, it is not necessary to inhibit a network that is not even formed. This result was described already for SUD: in the case of abstinent heroin users, cue-reactivtiy related simultaneous activity was found in prefrontal inhibitory regions (dlPFC), the OFC and mesolimbic structures (Li et al., 2012). This activation of the whole network is discussed in terms of high relapse vulnerability, and highlights its clinical relevance. A higher fronto-striatal functional connectivity can also be found in cocaine use disorders (Wilcox et al., 2011). These fMRI results implicate higher connectivity between OFC and dlPFC with subcortical structures for cocaine-related in comparison to other addictive stimuli. Although our fNIRS measurements were restricted to cortical areas, our functional connectivity results are still in line with findings from fMRI studies, implicating fNIRS as a valid method to measure neurophysiological correlates of cue-reactivity.

A more fine grained exploratory analysis of the separate tasks during the cue exposure revealed interesting group effects in relation to cue exposure time course. Connectivity between both hemispheres differed between smokers and controls already at the beginning of the task. Moreover, increased connectivity of OFC and dlPFC was observed during the smelling task in smokers. Interestingly, directly following this task segment, a group difference occurred for HHb concentrations within the OFC. Whether the increased connectivity between OFC and dlPFC in smokers directly underlies the following reduction in OFC activation during cue exposure should be further investigated. On a theoretical level, it seems to confirm a model of the dlPFC as a cognitive control structure down-regulating addiction-related activity

within reward structures of the brain (with increased connectivity, i.e., co-activation between both areas as the first step of such a process).

Studies of cue-reactivity in abstinent alcohol-dependent subjects have already been conducted with fNIRS (Dempsey et al., 2015). The authors found that time of abstinence was negatively correlated with activation in dlPFC and dorsomedial PFC. Also in prescription-opioid dependent subjects fNIRS was applied to detect prefrontal activation related to cue-reactivity (Bunce et al., 2015). The authors found a correlation of fNIRS activation in the dlPFC and the number of days since the last consumption indicating a re-regulation of the dysregulated reward-system. The promising results indicate the validity of fNIRS as a measure for neurophysiological correlates of cue-reactivity.

Yet another important aspect we found was the timing issue. Activation of the OFC was not specific to smokers, but rather appeared earlier in smokers in comparison to controls. Likewise, in the subjective craving ratings, we see changes that are not linear during the cue exposure, but rather inversely u-shaped. This is a known time course of subjective craving from clinical applications of CET and therefore highlights the importance of timing for the cue-reactivty magnitude. One of the major goals for clinical application of CET is that patients learn about this relationship and experience a decline in craving at its most intense point, while resisting compulsive behaviors. In summary, extending the time to a reaction in a cue exposure situation seems to be desirable.

Importantly, when translating an experiment to clinical implications, inter-individual differences of cue-reactivity in SUD patients need to be addressed. A study focusing on cue-reactivity in alcohol dependent patients revealed only 22% of the sample exhibiting cue-reactivity on both a physiological and subjective level, 42% having only a physiological response and 31% without any sign of cue-reactivity (Szegedi et al., 2000). Moreover, a study with former cocaine users did not find significant differences to controls in cue-reactivity or activation in inhibitory regions at the group level, but on the level of a minority of individual participants (Bell et al., 2014). This result highlights the importance of considering inter-individual differences in studies on cue-reactivity. At this point, the need for diagnostic tools to capture those high risk patients arises. Therefore, the validity of methods and parameters used for the assessment of cue-reactivity needs to be further approved in clinical samples as well.

Although our results are promising concerning the validity of cue-reactivity measurement with fNIRS during *in vivo* CE, several limitations need to be addressed. As the study was conceptualized as a pilot study, a relatively small sample was assessed. Moreover, the sample of smokers is inconsistent with respect to smoking habits and is constituted of occasional, rather than dependent, smokers. Nevertheless, 25% of the subjects were heavy smokers. As a consequence, there was no explicit smoking deprivation, which would have led to greater differences in this rather heterogeneous group. The stimulus set was standardized, resulting in the same objects/ cigarette brands for every subject. Stimuli individualized according to smoking habits might be even more effective to induce cue-reactivity.

A further important point to consider is the lack of a control condition. We chose a naturalistic cue exposure situation as experimental setting, implying shortcomings on the inference of measured activity to specific processes during cue-reactivity. Such effects have to be further investigated for a better understanding of the specific processes contributing to the effect we found.

We could clearly see a difference in prefrontal functional connectivity and subjective craving ratings between smokers and controls. Nevertheless, those are the only two aspects of cue-reactivity we assessed. For future studies, it would interesting to gain additional information on further levels, e.g. physiological responses or the smoking behavior of a subject after a CET session. Regulation of the autonomic nervous system is generated subcortically. Additional measurements of autonomic nervous system parameters like HRV (Garland et al., 2012) or skin conductance level (Gray et al., 2011) therefore provide valuable supplementary information about subcortical activity during cue exposure in SUD. Such methodological combinations could attenuate the shortcomings off NIRS' spatial measurement restriction to the cortical surface.

A better understanding of cortical regions activated within the cue exposure time course and successful inhibition of consumption yields positive future perspectives for the treatment of SUD: the dlPFC is a region of interest for neurostimulation, arising from literature investigating cue-reactivity (Dieler et al., 2014). However, further rTMS studies focused on activation of the dlPFC are needed to elicit the exact stimulation parameters for maximal effect (Gorelick et al., 2014). A better understanding about alterations in prefrontal activation patterns in subjects with SUD should also contribute to more efficient neurostimulation approaches.

Another very promising approach to the treatment of SUD is fMRI neurofeedback training for the regulation of motivation valence in visual stimuli (Sokunbi et al., 2014). Feedback is driven by activation in reward related brain structures and implemented by manipulating the size of a visual cue and therefore reflecting approach (big) versus avoidance (small) behavior. Implementation of such a neurofeedback approach into an fNIRS setting could provide further ecological validity, as the context is less alienating then in an MRI scanner (e.g. lying, narrowness, noise). Therefore, our results on fNIRS measures of cue-reactivity are promising not only for diagnostic issues but likewise for future perspectives of fNIRS as a useful therapeutic tool, e.g. implementing neurofeedback in patients with SUD.

## 6. Study 4: Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure

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Kroczek, A. M., Häußinger, F. B., Rohe, T., Schneider, S., Plewnia, C., Batra, A., Fallgatter, A. J., & Ehlis, A.-C. (2016). Effects of transcranial direct current stimulation on craving, heart-rate variability and prefrontal hemodynamics during smoking cue exposure. *Drug and Alcohol Dependence*, *168*, 123-127.

**6.1 Abstract**

*Objective:* Drug-related cue exposure elicits craving and risk for relapse during recovery. Transcranial direct current stimulation is a promising research tool and candidate treatment for relapse prevention. Enhanced functional neuroconnectivity is discussed as treatment target. The goal of this research was to examine whether transcranial direct current stimulation affected cortical hemodynamic indicators of functional connectivity, craving, and heart rate variability during smoking-related cue exposure in non-treatment-seeking smokers.

*Method: In vivo* smoking cue exposure supported by a 2mA transcranial direct current stimulation (anode: dlPFC, cathode: OFC; placebo-controlled, randomized, double-blind) in 29 (age: *M*=25,*SD*=5) German university students (at least smoking once a week). *Cue reactivity* was assessed on an autonomous (HRV) and a subjective level (craving ratings). Functional near-infrared spectroscopy measured changes in the concentration of deoxygenated hemoglobin, and seed-based correlation analysis was used to quantify prefrontal connectivity of brain regions involved in cue reactivity.

*Results:* Cue exposure elicited increased subjective craving and HRV changes in smokers. Connectivity between the OFC and dlPFC was increased in subjects receiving verum compared to placebo stimulation (*d*=0.66). Hemodynamics in the left dorsolateral prefrontal cortex, however, increased in the group receiving sham stimulation ($\eta^2$=.140). Transcranial direct current stimulation did not significantly alter craving or HRV during cue exposure.

*Conclusion*: Prefrontal connectivity – between regions involved in the processing of reinforcement value and cognitive control – was increased by anodal transcranial direct current stimulation during smoking cue exposure. Possible clinical implications should be considered in future studies.

## 6.2 Background

Substance use disorders are related to compulsive consumption patterns, established by repeated connections of the reinforcing value of a drug of abuse to its contexts and features (referred to as cue). In studies on addiction, this effect is termed cue-reactivity and reflects the expression of the retrieved addictive memory triggered by substance-related cues. It is expressed on a subjective (craving) or autonomous (e.g. HRV) level (Carter & Tiffany, 1999). During alcohol (Rajan et al., 1998) and smoking (Erblich et al., 2011) cue exposure the low frequency (LF, regulated by sympathetic nervous system) and high frequency (HF, regulated by parasympathetic mechanisms) power spectra peaks of the HRV were found to be increased. Functional neuroimaging studies reveal cue-related activation in SUD in limbic and prefrontal regions, including the ventromedial prefrontal cortex, the OFC and the basolateral amygdala (Heinz et al., 2009; Kuhn & Gallinat, 2011; Schacht et al., 2013). OFC is involved in the processing of reinforcing values while the amygdala is related to autonomic responses (Heinz et al., 2009). Additionally, there are studies finding decreased functional connectivity of reward-related (OFC) and inhibitory regions (PFC) in substance use disorders (Filbey and Dunlop, 2014; Janes et al., 2010; Zhang et al., 2011).

Functional near-infrared spectroscopy (fNIRS) is an optical imaging method rapidly gaining importance in psychological research (Ehlis et al., 2014). Hereby, hemodynamics can be measured on the cortical surface (2-3 cm depth, Haeussinger et al., 2011), assessing the concentration changes of oxygenated and deoxygenated hemoglobin. Activity changes in OFC and dlPFC captured by fNIRS are related to SUD (Ernst et al., 2013). NIRS is also applicable during a realistic in vivo cue-exposure (Kroczek et al., 2016), as it allows small movements in an upright position.

This pilot project was designed to establish a combined tDCS/cue exposure protocol to capture changes in cortical hemodynamics as foundation for a relapse prevention treatment in clinical populations. The suitability of tDCS in craving reduction or changes in activity of prefrontal regions was recently investigated in SUD (Boggio et al., 2008; Conti et al., 2014; da Silva et al., 2013; Herremans & Baeken, 2012). Both the remote activation of midbrain structures after dlPFC activation (Chib et al., 2013) and the effect of the current psychological state (Plewnia et al., 2015; Shahbabaie et al., 2014) have to be considered in such studies.

In this pilot study, we investigated effects of prefrontal tDCS during smoking cue-exposure on craving, sympathetic and hemodynamic activity measured by fNIRS. Furthermore, we were

interested in tDCS effects on connectivity of the OFC and dlPFC during cue-exposure in smokers. We expected higher functional connectivity between OFC and dlPFC along with lowered craving and decreased sympathetic activity (reduced low and increased high frequency band power peaks and a reduced low/high frequency ratio) related to tDCS (anode: left dlPFC, cathode: OFC) during cue-exposure in smokers.

## 6.3 Methods

### *6.3.1. Participants*

29 smokers were assigned to group (verum vs placebo) randomly and double-blind. Two subjects per stimulation group were excluded due to insufficient fNIRS data quality (verum: n=13; placebo: n=12). Amount of smoked cigarettes per week did not differ between verum (*M*=34, *SD*=45) and placebo group (*M*=35, *SD*=37), $t_{23}$=-0.062, *p*=.95. FTND (Heatherton et al., 1991) scores were 0 in 13 subjects (verum:6, placebo: 7) and 1-7 in 12 subjects. Duration since the last cigarette varied between 0.25–187 h (*M*=33 h, *SD*=50), not differing according to stimulation group ($t_{25}$= .10, *p*=.28). Groups did not differ with respect to gender (verum: 8 female, 4 male; placebo: 7 female, 6 male, $\chi^2$=.43, *p*=.51) or age (verum: *M*=26 years, *SD*=4; placebo: *M*=24 years, *SD*=3, $t_{17}$=1.44, *p*=.166).

### *6.3.2 tDCS*

A 15 minutes tDCS (constant 2 mA, 10s fade-in/fade-out) was applied by a CE-certified stimulator (DC-STIMULATOR MC, NeuroConn GmbH, Ilmenau, Germany) using a pair of 5×7 cm rubber electrodes placed over F3 (anode) and Fp2 (cathode). In the placebo group, fading in and immediate fading out elicited a tingling sensation resembling the verum stimulation without brain effects (Gandiga et al., 2006). 6 subjects stated having received placebo stimulation (verum: 3, placebo: 3) and 19 subjects stated having received verum stimulation (verum: 10, placebo: 9) in the treatment check at the end of the experiment, without difference in distribution between stimulation groups ($\chi^2$=.013, *p*=.637).

*6.3.3 HRV*

Electrocardiogram was acquired using a BrainAmp ExG amplifier and Brain Vision Recorder software (Brain Products Inc., Munich, Germany) at 500 Hz. R-R waves were automatically detected using Kubios 2.0 (Biosignal Analysis and Medical Imaging Group, University of Finland). LF and HF band power peaks of HRV and the low/high frequency ratio were analysed.

*6.3.4 fNIRS*

We used the ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) with 31 NIRS optodes (13 light sources, 12 detectors, channel array 3 cm inter-optode distance, 10Hz sampling rate . Assignment of NIRS channels to their corresponding cortical regions in MNI space located underneath, was conducted using neuronavigation [NeuroConn, Ilmentau, Germany] on a physical head model of the ICBM-152 brain and its transfer to corresponding cortical projection points on the ICBM-152 brain template (Cutini et al., 2011). Hence our regions of interest were CH48 (OFC), CH50 (left BA46), CH2, CH3, CH4, CH5 (right BA9) and CH6, CH16 (left BA9).

*6.3.5 Procedure*

The *in vivo* cigarette cue-exposure with verbal instructions by the examiner lasted 20 minutes with tDCS starting with a one minute delay. Subjects were instructed to focus on changes in subjective perceptions and rated craving verbally every 2 minutes on a scale from 0 (no urge to smoke) to 10 (very strong urge to smoke). Instructions gradually increased in intensity (see supplementary material). Afterwards, subjects judged their stimulation group assignment.

*6.3.6 Preprocessing of fNIRS data*

Deoxygenated hemoglobin was bandpass filtered (0.008–0.5 Hz) and movement-corrected by a wavelet filter approach (Molavi & Dumont, 2012) implemented in Wavelab 850 (http://statweb.stanford.edu/~wavelab/).

For the analysis of the time courses, mean level of baseline-corrected levels of deoxygenated hemoglobin during the 20 minutes cue-exposure were extracted into 30 bins

for a total of 20 minutes cue-exposure for OFC (left BA11) and the dlPFC (left and right BA9 and left BA46). When concentration differences between adjacent bins exceeded 0.2 mm*mmol/l, it was considered as a mechanical artifact and a spline interpolation was conducted. Analogously heart rate variability was analyzed dividing the time course by four.

*6.3.7 Statistics*

HRV and deoxygenated hemoglobin in left BA11, BA9 (left and right) and left BA46 was analyzed by repeated measures analyses of variances with time (4 bins) as within-subject factor and stimulation (verum vs. placebo) as between-subjects factor. The analysis of craving included 10 ratings. For connectivity analysis, we correlated time series for the seed channels (CH48, CH6) with each time series of the remaining 31 channels (seed-based correlation analysis). Randomization test was used to test statistical effects.

## 6.4 Results

There was a main effect of time on craving ($F_{3, 78}$=29.65, $p$<.001, $\eta 2$=.091, cf. Fig1a), but no interaction with stimulation ($F_{3, 78}$=0.80, $p$=.514, $\eta 2$=.033). The percentage of low-frequency power spectra peaks increased during smoking cue-exposure ($F_{3, 69}$=5.87, $p$=0.001; $\eta^2$=.20, cf. Fig1b) significantly from the first to the second measurement interval, $t_{24}$=3.6, $p$=.002. There was no significant time x stimulation interaction ($F_{3, 69}$=1.64, $p$=.187, $\eta 2$=.067) for low-frequency power spectra peaks. There were no significant effects for the low/high frequency ratio (time: $F_{3, 69}$=0.28, $p$=.838, $\eta 2$=.012, interaction: $F_{3, 69}$=0.28, $p$=.841, $\eta 2$=.012) and high frequency power spectra peaks (time: $F_{2, 48}$=0.71, $p$=.500, $\eta 2$=.030, interaction: $F_{2, 48}$=0.41, $p$=.671, $\eta 2$=.018).

A stimulation × time effect in left BA9 ($F_{2, 48}$=3.26, $p$=0.039, $\eta^2$=.140) reflected a decrease after the first interval in the placebo group (Fig. 1b). Connectivity of CH48 and CH6 was increased (effect size 0.66, cf. fig2) for verum compared to placebo stimulation, $p$<.001. There was not a statistically significant correlation between craving and heart rate variability.

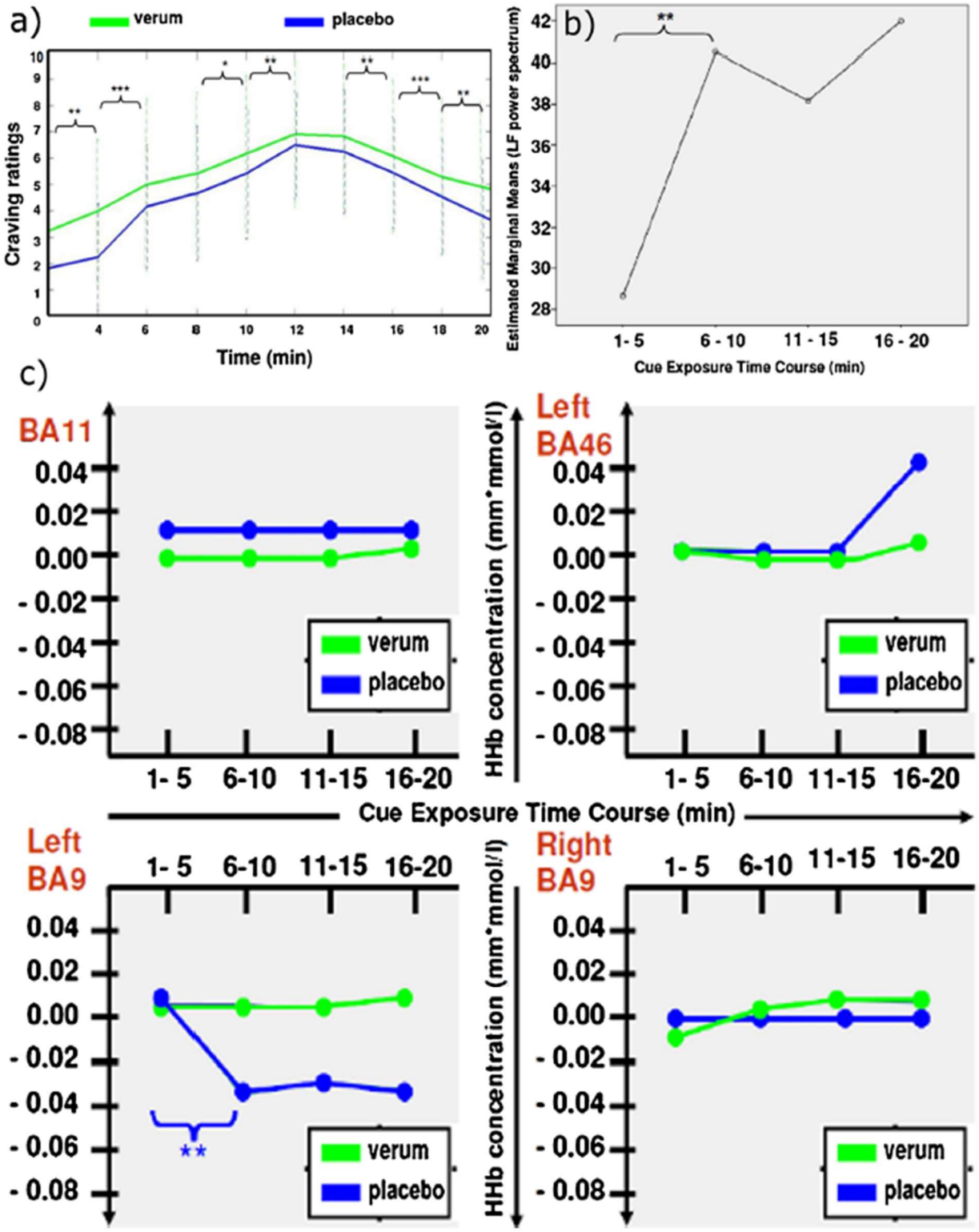


Figure 14 Cue exposure time course a) craving b) low frequency power spectrum peaks (LF) c) fNIRS. Significant decline and increase is indicated with asterisks: p<.05 *, p >.01**, p<.001***

## 6.5 Discussion

The present study investigated the immediate effects of tDCS during an *in vivo* smoking cue-exposure in smokers measuring prefrontal hemodynamics, heart-rate variability and craving. Furthermore, we investigated tDCS-related changes in functional connectivity of the OFC (processing reinforcing value of a stimulus) with the dlPFC (involved in inhibitory control of an automatic response). TDCS was applied to the dlPFC to strengthen cognitive control during cue-exposure induced OFC activation (Falcone et al., 2016).

Indeed, tDCS increased functional connectivity between the dlPFC and the OFC in verum-stimulated smokers. Hence our electrode placement did not up-regulate hemodynamics in the dlPFC or attenuate hemodynamics within the OFC independently, but rather enhanced coupling between those regions. This result suggests that tDCS influences hemodynamic coupling during smoking cue-exposure within an addiction-related cortical network, which was found in a prior study to differ in smokers compared to non-smoking controls (Kroczek et al., 2016).

Analyzing deoxygenated hemoglobin in the dlPFC and the OFC separately revealed a conspicuous effect of time during placebo stimulation only. Increased hemodynamic activity in the dlPFC was related to sham stimulation while active tDCS was related to increased connectivity of OFC and dlPFC. Subjects were instructed to intensify their craving throughout the cue-exposure, targeting OFC activity. Simultaneously applied anodal prefrontal tDCS did not lead to an increase in dlPFC activation, but instead resulted in a strengthened interplay between valence-related (OFC) and control-related (dlPFC) structures.

Furthermore, we did not find the expected time × treatment interaction on craving or heart-rate variability. Given the pilot character of our study, the power of 0.482 (for effect size cf. (Boggio et al., 2008) indicates a high probability to miss a given tDCS effect (β-error). Additionally, the subjective craving measure (on a relatively course, 10-point Likert scale) might be too insensitive to capture the possibly subtle effects of an excitatory tDCS on craving in habitual smokers. Clinical studies of addiction and/or pilot studies employing finer cue-reactivity measures in terms of, e.g., an attentional bias paradigm (Field et al., 2011) could provide further information.

*Limitations*

As near-infrared light cannot penetrate the black tDCS electrodes we could only assess hemodynamics at the borders of, and adjacent to, the tDCS electrodes. Furthermore, we

placed an active tDCS reference site onto the head, complicating the interpretation of tDCS effects: both a facilitory effect within the left dlPFC or inhibition of the OFC (or a combination of both) could be the neural basis of alternations in cue-reactivity.

Due to the preliminary nature of the study, our sample size was quite small and characterized by wide variation in smoking levels. The sample consisted of everyday smokers as well as occasional smokers. Nevertheless, the total amount of consumed cigarettes per week did not differ significantly between stimulation groups. In future studies, it would be interesting to analyze whether consumption patterns modulate the tDCS effects, e.g. comparing heavy smokers to occasional smokers. Yet the results of the present study are promising for future investigations of the mechanisms underlying relapse prevention in substance use disorders. Specifically, they give a first indication of the neuronal basis underlying facilitating prefrontal stimulation protocols that have been proposed as complementary neurobiological addiction treatment.

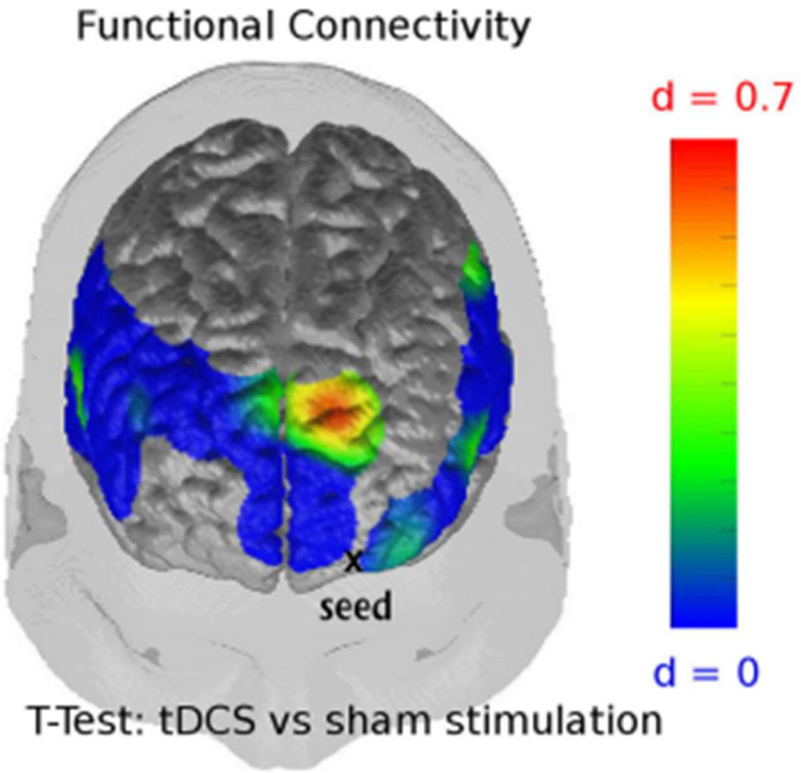


**Figure 15** Seed-based correlation analysis for CH48 (OFC). Stimulation effect sizes are depicted. Connectivity between CH48 and Ch6 is increased in subjects receiving verum stimulation.

## 7. General Discussion

Within this work, automatized processes related to cue-reactivity and their interplay with cognitive control were assessed in HD (**Study 1** and **Study 2**) and smokers (**Study 3** and **Study 4**). Aiming at a better understanding of the interplay of automatized (cue-reactivity) and deliberative (cognitive control) process contributes to the discussion concerning developments in the transition of automatized to deliberative behaviors with implications for SUD treatment. In the following, the findings from the presented four studies will be summarized on the background of this scientific aim.

Within the HD and LD population in the visual beverage classification paradigm of **Study 1,** Hypothesis 1 was partially confirmed: Alcohol cue-reactivity was found specifically in HD, reflected in increased LPP amplitudes. P100 was modulated in latency, but not intensity (amplitude). Alcohol-related cues were processed faster than non-alcoholic control stimuli. This finding confirms cue-reactivity at an automatized and evaluative cue-processing stage. Within the same sample, hypothesis 2 was confirmed, as there were no differences in processing of color of beverage pictures without content information. This finding approves the validity of the cue-reactivity measurements elicited by the visual stimuli in a HD sample. Therefore, the visual beverage cues were used again for the investigation of cue-reactivity effects on performance monitoring within **Study 2**. In **Study 2**, hypothesis 3 was confirmed, as HD depicted deficiencies in error monitoring in alcohol-cued trials. However, data **from Study 2** did not support Hypothesis 4, as there was no group difference between HD and LD in dlPFC activity. However, in the overall sample, we observed increased dlPFC activity independent of cues in trials after errors. In the HD sample, alcohol dependency was explicitly excluded. Cognitive control was diminished especially in patients with SUD, therefore this finding can be integrated in the perspective of HD as consumers with cue-reactivity but still compensatory mechanisms in cognitive control in contrast to subjects with substance dependency. The following hypotheses were therefore tested in subjects not only in subjects with a highly frequent consumption pattern like HD but likewise addicted individuals. For practical reasons, to involve addicted subjects, another substance was focused, namely nicotine. Therefore, results from **Study 3** and **Study 4** were captured in samples of regular smokers and smokers with nicotine dependence. Another advantage of a smoking sample is the criterium for controls. While LD had rare alcohol drinking experience, controls for the smoking population had no smoking experience at all. This difference has practical reasons, as due to the high

popularity of alcohol in our society, individuals without any alcohol consumption experience during life-time is very rare.

Therefore smoking individuals were compared to never-smoking controls within **Study 3**, partially confirming hypothesis 5: differences between smokers and controls during smoking cue-exposure did not affect OFC activity per se, but did affect its timing. OFC was activated in smokers by the sight of smoking cues, while OFC activity increased in controls by the instruction to make own attempts to increase smoking craving, which however was not reflected at a subjective level according to craving ratings. Controls did not report craving. As hypothesized, craving was elicited in smokers, nonetheless. Nobody smoked during smoking cue-exposure; therefore, smoking behavior was inhibited successfully. We focused on the dlPFC as the region related to behavioral inhibition to craving, finding lower maximum craving in subjects with increased dlPFC activity. Still we could not confirm group differences in dlPFC activity (Hypothesis 6). Nevertheless, group differences occurred in connectivity of OFC and dlPFC. Connectivity between the OFC – a region involved in processing emotional value – and the dlPFC – a region involved in processing cognitive control – was increased in smokers during smoking cue-exposure, which fits quite well in current neuroscientific models.

The following conclusions resulted from a sample of smokers, as **Study 4** focused on the modulation of cue-reactivity and cognitive control during an active tDCS of the dlPFC compared to a sham stimulation. By means of this intervention, the connectivity highlighted in **Study 3** was increased by anodal tDCS applied to the dlPFC. Nevertheless, the assumptions about immediate tDCS effects on prefrontal brain activity could not be confirmed: There was no tDCS effect on craving, HRV or OFC activity (Hypothesis 7). Furthermore, contradictory to our hypothesis, dlPFC activity was decreased during tDCS (Hypothesis 8). Still the tDCS induced modification of connectivity supports a promising discussion for SUD treatment approaches.

Within this dissertation, I considered the interplay of automaticity and deliberation from a “mindful perspective”. This general discussion involves developments in cue-reactivity paradigms and measurements as an approach for a better understanding of automatized processes. Additionally, this dissertation focused on cognitive control mechanisms. Simultaneous fNIRS-EEG measurements were conducted to analyze cognitive control processes with high temporal (EEG) and spatial (fNIRS) resolution. Although this approach is promising, some methodological concerns need to be discussed.

Furthermore, there is a discussion considering modifications of the interplay of automatized and deliberative processes induced by cue-exposure and tDCS application. Due to the pilot-study characteristics, the replication in further samples is necessary. Nevertheless, the transfer to SUD treatment will be discussed, providing implications for further research.

### 7.1 Conclusion 1: Eliciting and measuring cue-reactivity in the laboratory

We measured cue-reactivity in HD (**Study 1/2**) and smokers (**Study 3/4**) with different methodologies. Visual alcoholic cues, presented for 350 ms, affected early attentional processing (P100) and motivational significance (LPP) in HD. This effect was related to content information (alcoholic vs non-alcoholic), not physical attributes of beverage pictures. This result encourages the use of individualized stimulus sets to maximize cue-reactivity in the laboratory. The establishment of individualized stimulus-sets is increasingly relevant for cue-reactivity research (Conklin et al., 2010; Jobes et al., 2015; Hartwell et al., 2016). It allows for an increase of ecological validity in cue-reactivity research.

A further effect of cue-reactivity was revealed in **Study 2**: Alcohol cues diminished error-monitoring (ERN/Ne amplitudes) in HD. Interferences of error-monitoring and cue-reactivity were measured accordingly. However, there was no effect on behavioral outcomes. Although there were some NIRS optodes in prefrontal regions, there was no evidence for compensatory mechanisms in prefrontal hemodynamics in **Study 2**.

For a better understanding of the compensating mechanisms, prefrontal hemodynamic activity was assessed using a probeset capturing broader prefrontal regions. In **Study 3/ Study 4**, cognitive control during cue-reactivity was assessed again, but with increased ecological validity, using an in vivo cue exposure paradigm. Increased connectivity of the dlPFC and OFC distinguished smokers from controls. Connectivity was even further enhanced by tDCS. Nevertheless, this result reflects the therapeutic intention of the intervention: subjects were instructed to accept craving, not to suppress it, or to distract themselves from it. Therefore, a regional increase of dlPFC activity could be related to cognitive distraction, which would not reflect the rationale of this intervention. Both studies using the in vivo cue exposure paradigm support the feasibility of the time course assessment of hemodynamic activity in dlPFC and OFC. This allows the investigation of the interplay of cue-reactivity and executive functioning in a realistic setting. NIRS has been shown to be a

valuable method to investigate decision making inside and outside the laboratory (Kopton & Kenning, 2014). Likewise, immediate tDCS effects on hemodynamic responses in the PFC have been investigated in healthy subjects during task performance in naturalistic settings, using portable NIRS (McKendrick et al., 2015). In summary, more realistic settings increase the ecological validity of neuroscientific investigations. Using this approach allows the involvement and modulation of context-factors.

Within this dissertation, different cue-reactivity levels have been assessed. In addition to hemodynamic activity during smoking cue-exposure, subjective craving and heart-rate variability were also assessed. Time course of sympathetic activity (assessed by HRV) differed from craving time course: while craving ratings usually declined within the 20 minutes of cue-exposure, sympathetic activity was still increasing. Therefore, there was no correlation between measures. This, again, highlights the importance of multidimensional assessments of cue-reactivity, and confirms the introduced independence of cue-reactivity levels. A multidimensional perspective needs to be considered, before evaluating a subject as non-responder to substance cues. Over-simplification of cue-reactivity in SUD research to a single level is misleading, as cue-reactivity effects could be underestimated.

The relationship between cue-reactivity measures and SUD severity differs according to the level of focus: While severity of dependence is related to increased physiological reactivity, it is independent of subjective craving. There is no significant difference in craving ratings between alcohol dependent patients and social drinkers (Glautier & Tiffany, 1995). One possible explanation is that SUD patients are more conservative in their ratings then subjects who have never experienced a very strong dependency-related urge before.

Within our sample of occasional smokers, however, there was a correlation of cue-reactivity and prefrontal activation; OFC activity correlated with craving variance. This is in line with the finding that OFC is involved in the processing of reinforcing value (Rudebeck & Murray, 2014). The relationship between reduced OFC activity and craving reduction has also been discussed as a potential target for neuromodulation (Hanlon et al., 2015). Maximum craving correlated negatively with dlPFC activity in **Study 3**, which indicated craving inhibition as functional meaning of dlPFC activity. However, Hayashi et al. (2013) proposed dlPFC activity as a reflection of intertemporal activity, therefore being a reflection of active cue-reactivity, not its inhibition. The perceived intertemporal availability needs to then be considered in further studies to elucidate that concern.

Still another factor to consider is that advanced in vivo measurements of prefrontal activity require appropriate analytical strategies. The intensity of the tasks during in vivo cue-exposure in **Study 3/ Study 4** increased while effects were prolonged, making classical event-related design unfeasible. Similarly, block design was also inappropriate, as blocks were not equal in intensity, and changes in time course were the main interest of the investigation. Therefore, individual time courses were analyzed using one minute bins. For this approach, thorough artifact-correction was fundamental, for which we evaluated different pre-processing approaches for fNIRS data (Brigadoi et al., 2014). After band-pass filtering, data was visually inspected to approve sufficient data quality. Channels with technical problems were excluded. In Study 3, bins were assigned to interpolation when they were two standard deviations above the individual mean of a person. The validity of this approach was then visually inspected by the approval of the common motion artifact pattern. For **Study 4**, motion artifact correction was further automatized using wavelet filtering, as was recommended in a direct comparison of several methods (Brigadoi et al., 2014).

Additionally, the prefrontal probe set used during cue-exposure was prone to arousal evoked physiological artifacts (Haeussinger et al., 2014). Therefore, deoxygenated hemoglobin was analyzed. Deoxygenated hemoglobin is more robust against arousal effects then oxygenated hemoglobin, at the cost of a decrease in signal intensity. In both Study 3 and **Study 4**, the effect sizes were large enough to use deoxygenated hemoglobin to prevent confounding arousal effects.

The straightforward time course analysis of deoxygenated hemoglobin revealed the importance of timing issues. Relevant differences between groups were found in the timing of activation and the interaction of brain regions, not in the activation in a single brain region. This further stresses the importance of connectivity analyses. A “mindful perspective”, even of a researcher, is helpful in this field for a thorough analysis of such data. Both studies revealed important group effects during in vivo cue-exposure that contrasted with connectivity measures. This effect is consistent with the literature: a sample of patients with alcohol dependency (compared to healthy controls) showed reduced cingulate cortex connectivity during the perception of alcohol and stress cues (Zakiniaeiz et al., 2017). Connectivity measures were related to subsequent alcohol relapse, revealing the validity of connectivity markers for behavioral outcomes. In a sample of smokers, decreased functional connectivity between the insula and the dlPFC correlated with relapse during the first day of

attempted smoking cessation after cue exposure (Zelle et al., 2017). Concludingly, current literature supports the validity of connectivity measures as cue-reactivity markers.

The multidimensional facets of cue-reactivity and its underlying neuroanatomical mechanisms have considerable parallels to emotions. Emotions are elicited by environmentally salient stimuli, reflecting the organism facing a challenge or opportunity (LeDoux, 2012). Like emotions, cue-reactivity has a behavioral implication (consumption), an autonomic component (increased sympathetic activity) and a subjective evaluation (craving). Emotion, cognition and perception are only theoretically separable (Lindquist et al., 2012); they are intertwined in decision making. In the studies presented in this dissertation, we observed changes in every aspect. **Study 1** revealed evidence for alcohol-cue modulations at the perceptive level. **Study 2** revealed effects on cognitive processes (error-monitoring). Increasing ecological validity in **Study 3/ Study 4** targeted the activation of broad parts of the emotional circuit. However, like emotions, those aspects need to be integrated for a thorough understanding. To relate emotions to cognitive processes, we assume that emotions are not only a modulator, but likewise a prerequisite for decision-making. A meta-analysis on neuroimaging studies analyzing emotions highlighted network-based assumptions for further studies (Lindquist et al., 2012). This approach for the understanding of the interplay of executive functioning and emotions is also valuable for the understanding of the relation of executive functioning to cue-reactivity. Connectivity analysis (which has been applied in **Study 3/ Study 4**, respectively) is a promising approach, unraveling the intertwined process of not only understanding an individual brain system, but also global brain functioning (LeDoux, 2012). Our findings are in line with current studies revealing emotional features in cue-reactivity, e.g. a memory bias for alcohol cues in social drinkers (Nguyen-Louie et al., 2016). This perspective needs to be considered for further research in the field.

### 7.2 Limitation and future directions 1:

The absence of a control condition is a limitation of the in vivo cue-exposure paradigm used for **Study 3 / Study 4**. The implementation of an adequate control condition is challenging. One reason concerns carryover effects elicited by cue-reactivity. Activating intense cue-reactivity in a context with high ecological validity needs some time to recover. In **Study 4**, we revealed that even though craving usually decreased within a 20 min time course,

autonomic response did not. A possibility to control for carryover effects in further studies are separated measurements for active and control conditions.

Additionally, the identification of appropriate parameters for each level of cue-reactivity must be addressed. During in vivo cue exposure, subjects rated craving verbally on a 0-10 scale (Study 3 / Study 4). However, authors like Kavanagh et al. (2013) considered a subscale of the (obsessive-compulsive drinking scale, OCDS (Anton et al., 1995) questionnaire as appropriate for craving assessments. Therefore, the predictive value of questionnaire-based craving ratings and cue-induced craving ratings has to be compared in further investigations.

HRV, which was assessed in **Study 4**, is another promising measure for the assessment of treatment response. Even biomarker characteristics of the HRV for the development of SUD have been discussed (Karpyak et al., 2014). Still, there are various parameters, reflecting different aspects of HRV, which should be related to their clinical relevance. The assessment of the clinical relevance is another shortcoming that is present especially in neuroimaging studies, which often neglect prospective behavioral outcomes. Even if behavioral outcomes are involved, their definition is not always clear-cut, e.g. the definition of relapse is often dichotomous. Communication and comparison of findings in the field is therefore limited and requires fine-grained clearly operationalized dependent variables. A fine-grained operationalization of relapse, however, allows regressive modeling to increase the predictive value of cue-reactivity markers. Such measures need to involve sober time preceding relapse, social drinking occasions not involving relapse, consumption amount, and consumption duration.

The need to involve overt behavior in the interpretation of brain activity was highlighted in **Study 2**. ERN/Ne amplitudes were decreased in error trials, without immediate effects at the behavioral level. Similarly, Mainz et al. (2012) found effects of alcohol cues on brain activity, without impairments in task performance in patients with alcohol dependency. The authors suggested floor effects as a possible interpretation. Another hypothesis is that compensatory mechanisms regulate cue-reactivity effects. Contradictory to our a priori hypothesis, however, we did not find compensatory dlPFC activity in **Study 2**. However, we found evidence for differences in error-monitoring and error-adaption strategies that will be discussed in the cognitive control chapter. Nevertheless, a better understanding of concrete

strategies to compensate cue-reactivity and to relate this to prospective behavioral data is vital.

Another shortcoming concerned all four studies: due to small samples, we only analyzed group differences between HD/LD and smokers/non-smokers, respectively. Unfortunately, there was no subtyping of HD and smokers, respectively, in “responders” and “non-responders” considering craving and autonomous response separately. Considering previous results on subtypes in alcoholics, results from the current studies probably underestimate cue-reactivity effects. It would be interesting for prospective research to relate individual cue-reactivity patterns (different levels of craving, autonomic response, behavior) to brain activity. Furthermore, the predictive value of the classification into “responder” and “non-responder” for the assignment of patients to psychotherapeutic interventions like cue-exposure therapy should be investigated.

Still, there is the question of how to interpret basic brain mechanisms in “non-responders”. A possible explanation is the lack of ecological validity (e.g. anxiety, depression, withdrawal) necessary to elicit cue-reactivity (Glautier & Tiffany, 1995). Cue-reactivity can automatically decrease, when a substance is obviously unavailable. Prospective cue-exposure paradigms should consider manipulating consumption possibility, requiring planning abilities related to dlPFC. Hayashi et al. (2013) suggested that the dlPFC activity was related to this intertemporal availability (expectation of substance availability) reflecting planning, rather than response inhibition. Therefore, the relationship between dlPFC activity and expectation of substance availability needs to be clarified and validated by prospective behavioral data (e.g. next consumption). The lack of such an assessment of prospective behavioral data (e.g. time to next consumption, intensity of consumption) is another short-coming within our studies. Nevertheless, this is an important point, as there was a large variance in consumption patterns within smokers, as some subjects within the sample had a nicotine-dependency while others were occasional smokers under definite circumstances (e.g. stress, parties). Furthermore, the HD / occasional smoker definition is not clear-cut in contrast to SUD dependency criteria, and there have been some different suggestions accordingly (Smith et al., 2017). In summary, further research on cue-reactivity is required, particularly its functional relationship to behavioral outcomes.

### 7.3 Conclusion 2: Disentangling cognitive control

Error monitoring is a prerequisite of cognitive control. There are different theories to explain the underlying mechanisms, of which the two most prominent (reinforcement learning theory and conflict monitoring hypothesis) have been introduced. On the one hand, data from **Study 2** supported the reinforcement learning theory: the presentation of visual alcohol cues before flanker stimuli did not alter the conflict, but rather reflected an outcome that is worse than expected, as no reinforcement (alcohol intake) occurred. On the other hand, the conflict monitoring theory was also supported, as increased dlPFC activity occurred after errors, independent of alcohol cues. Therefore, data suggests an integration of both theories to explain the increases in cognitive control and behavioral adaption.

However, data revealed differences in error-adaption strategies. PES was more unspecific than post-error response inhibition, which was related to decreased response-conflict amplitudes (reflected in decreased N2 amplitudes). PES, as an overt behavioral response, is an unspecific orienting response, reflecting interferences of task preparation due to insufficient suppression of irrelevant stimulus feature processing. Post-error reduction of interference, on the other hand, was related to specific increases of inhibitory control mechanisms (King et al., 2010). Both mechanisms were dissociated in terms of reactive and proactive error adaption (Kemper et al., 2016). Proactive error-monitoring allows task-specific facilitation, which was assessed as improved performance in congruent trials after congruent trials (Forster & Cho, 2014). In **Study 2**, we found diminished N2 amplitudes in LD in trials after correct responses, which was discussed as increased efficiency. Increased N2 amplitudes in HD, were then interpreted as compensatory response to achieve the same behavioral outcomes as LD. A different working group (Smith et al., 2015) also reported such findings. We interpreted N2 amplitude as a measure for the need of cognitive control in conflicts (Luijten et al., 2013). Consequently, constant N2 amplitudes in **Study 2** are related to decreased flexibility of adaptive processes in the HD sample, being related to unspecific compensation (Luijten et al., 2013).

Nevertheless, the most consistent findings in SUD were a decreased N2, decreased Pe and ERN/Ne amplitudes, and hemodynamic hypoactivity in the ACC, the inferior frontal gyrus and the dlPFC (Luijten et al., 2014). The ACC was evaluated as one of the core targets in SUD therapy. Our data revealed an impaired ERN/Ne, a potential generated in the ACC. Still, behavioral outcomes during the experiment were not significantly altered. HD did not reveal

general deficits in cognitive control related to a general ERN/Ne decline, impairments in dlPFC activity, or deficiencies at the behavioral level. The lack of an effect at the behavioral level is different from many studies in SUD. However, results from **Study 2** are in line with findings reported by Franken et al. (2017). We concluded an unspecific behavioral adaption strategy in alcohol-cued trials in HD. Nevertheless, this needs to be confirmed by an individualized analysis approach to capture strategies at a single-trial level.

### 7.4 Limitation and future perspectives 2:

**Study 2** indicated differences in error-adaption strategies. Nevertheless, averaging trials across the whole experiment neglects the individual time course of the responses. Our data revealed decreased hemodynamic dlPFC activity in trials before response errors and therefore confirmed the importance of the activation time course. Single-trial analysis allows to unravel task-related predictors more individually than based on general strategy, as revealed by the averaged response over all trials of a task condition. This approach could prevent an over-simplification of our model of performance-monitoring. However, interpreting data at a single-trial basis requires the technical implementation of adequate artifact correction methods. Additionally, an analysis at single-trial level has a benefit for combined EEG-fNIRS measurements. Both the high temporal resolution of EEG and the high spatial resolution of fNIRS can be related individually. This approach allows us to verify the validity of measurements for differences in cognitive control strategies. Moreover, the analysis of precursor states at a single-trial level could potentially predict the probability of errors. Data from **Study 2** and current literature highlights more complex relations during action-monitoring than previously assumed. Therefore, this single-trial approach could provide information previously neglected. For example, dynamic coupling of EEG and fMRI (Debener et al., 2005) is one possible approach to capture such complex relations. Single-trial analysis revealed a sustained negativity, which differed significantly at baseline before flanker onset (Eichele et al., 2008). Such studies emphasize the worth of information that is potentially lost in classical averaging analysis.

However, even besides analytic strategies, there is something to address considering the study design. **Study 2** lacked an efficiency measure for error adaption strategies. With respect to ego depletion, this needs to be assessed by an additional dependent variable. Ego

depletion is the decrease in behavioral performance in a second task following a task exploiting cognitive control (Baumeister et al., 2007; Inzlicht et al., 2014). One possible measure is an additional task, e.g. ratings of emotional content (Wiesener & Lindner, 2017), after a task demanding cognitive control. Furthermore, the influence of state variables should be assessed more systematically. In line with the importance of context, study results reveal significant effects of mindfulness induction before the task as well as increased ERN/Ne (Saunders et al., 2016).

### 7.5 Conclusion 3: Modulating cue-reactivity and cognitive control

To allow improvements in relapse prevention in SUD, it is helpful to understand the underlying mechanisms of both the dysfunction and the intervention. Smoking cue-exposure, the intervention applied in **Study 3**, modulates the relationship between cue-reactivity and cognitive control. Psychotherapeutically, results were encouraging: Cue reactivity and cognitive control were simultaneously evoked, reflected in increased connectivity of OFC and dlPFC during cue-exposure. Craving increased and declined within the 15-20 minutes cue exposure duration, a finding in line with experiences from clinical practice. In contrast, sympathetic activity, which was likewise evoked, did not recover within the 20 min time course. This is evidence for a faster recovery of subjective appraisal (craving) compared to the autonomic response. Therefore, if we only consider craving, patients are at risk to underestimate their own relapse vulnerability. To overcome this problem, cue-exposure therapy (CET) aims at the conscious perception of unconscious processes, like the physiological component of cue-reactivity. If only driven by automaticity, decision-making is at risk to be modulated unconsciously. Accordingly, mindfulness aims at the perception of the behavioral tendency automatically implicated (consumption) without immediate execution of action. Capturing automatized processes (cue-reactivity) involving cognitive control allows the transition to deliberate decision-making. This conscious perception of automatized processes is trained with mindfulness practice.

Another intervention aiming at a modulation of cue-reactivity and cognitive control within **Study 4** was tDCS. This non-invasive brain stimulation method is increasingly found to produce treatment effects in psychiatric diseases (Kuo et al., 2017). We used fNIRS to assess the immediate tDCS effects on cue-reactivity and cognitive control in smokers. fNIRS is a

convenient method for the assessment of immediate tDCS effects on cortical hemodynamics (Muthalib et al., 2013; Zama & Shimada, 2015; Jones et al., 2015). Measuring immediate tDCS effects on hemodynamics facilitates identification of optimal stimulation parameters. In **Study 4**, active dlPFC activity was reduced in comparison to sham stimulation. Comparatively, reduced cortical activity during tDCS can be interpreted as more efficient processing during comparable motor output (Muthalib et al., 2013).

Furthermore, we found a tDCS effect on increased functional connectivity between the OFC and the dlPFC. tDCS seems to enhance simultaneous activation of cue-reactivity and cognitive control. fMRI measurements report increased connectivity measures after tDCS as well (Yu et al., 2015). Furthermore, a study using a motor task revealed increased interhemispheric resting-state connectivity and increased flexion speed after anodal tDCS of the motor cortex (Kahn et al., 2013). Once more, the importance of connectivity measures was highlighted.

tDCS allows the modification of a transmitter system locally, which can be considered an advance over the global modification via pharmaceutical interventions. Current investigations on personalized assignments for therapeutic brain stimulation increase the specificity of treatment even further (Fettes et al., 2017). Due to neuroadaptive processes related to the persistence of drug-seeking behavior in SUD, the dlPFC, the OFC and the ACC are convenient target regions for further assessment in SUD research (Feil et al., 2010).
However, as already mentioned, valid parameters with predictive value for response to tDCS-supported cue-exposure therapy still need to be identified. A thorough assessment of cue-reactivity at its various levels and prospective behavioral data is required to establish such parameters. Although the described approach is very promising, there are some issues for the modulation of cue-reactivity and cognitive control that need to be addressed.

### 7.6 Limitation and future perspectives 3:

Although the current results are promising and a straightforward rationale for cue-exposure therapy, there is no consistent evidence for the efficacy of CET as currently implemented (Conklin & Tiffany, 2002). Therefore, optimal CET parameters need to be identified concerning, e.g., timing between sessions. Nevertheless, the high context-dependency of extinction learning remains a challenge for the use of CET in relapse

prevention. To allow generalization of the effects, context has to be as realistic as possible. Furthermore, there should be various high-risk situations. Unreinforced drug-administration is one possibility to create a realistic situation for extinction learning. A cigarette without nicotine or an alcohol-free beer are practical examples for unreinforced drug-administration. Virtual reality exposure is another approach to increase ecological validity. Preliminary data showed a reduction of cue-reactivity in subjective (craving ratings) and physiological (skin conductance) measures during virtual reality CET in smokers within four sessions (Choi et al., 2011). This study revealed that the interpersonal interaction within the scenarios, especially, elicited cue-reactivity. In our studies, participants received verbal instructions by the examiner. Nevertheless, interpersonal interaction was limited. Furthermore, interpersonal interaction could help to elicit cue-reactivity even in patients with strong avoidance tendencies. A problem during CET in SUD patients is decreased self-efficacy, which is probably related to the aversive nature of cue-reactivity. As usual in patients, cue-reactivity is closely related to relapse; patients tend to avoid cue-reactivity even during CET. Clinical practice reveals that coping strategies for regulation of cue-reactivity resemble strategies for the regulation of aversive emotions (e.g. distraction). Another parallel of cue-reactivity to emotions is the impairment of regulation during high stress levels. Stress is another factor highly related to relapse in addiction (Back et al., 2010; Koob, 2008). The induction of physiological stress (e.g. with the Trier Social Stress Test, TSST) is one possible intervention to intensify cue-reactivity in the laboratory and clinical setting.

Another limitation that has to be addressed is the transfer of our results from a high-risk consumer population to SUD populations. Our results need to be verified in samples with SUD. However, there was evidence for comparable cue-reactivity brain responses in intermittent and daily smokers (Shiffmann et al., 2013). Still, there is evidence for reduced resting-state connectivity of dlPFC and OFC in subjects with heroin dependency (Ma et al., 2010). Therefore, tDCS-induced increases in functional connectivity during CET need to be confirmed in an SUD sample and compared to high-risk consumers. Thus, the lack of smoking pattern subtyping is considered a limitation of **Study 3/ Study 4**.

Motivation to change, a factor related to modulations of cue-reactivity, was also neglected in the current studies (Courtney et al., 2016). There is evidence for a mediator effect of motivation on tDCS effects, e.g. on working memory improvements in fNIRS activation patterns (Jones et al., 2015). Again, it is important to assess additional parameters at the

behavioral level (e.g. time to next consumption, consumed amount of substance during relapse) to relate them to brain response patterns. This allows the analysis of the predictive value of abstinence motivation and cue-reactivity markers with clinical relevance. Those markers are necessary to evaluate treatment effects of SUD relapse prevention. Individualized intervention assignment for CET in subjects with increased cue-reactivity is a long-term goal. Nevertheless, this requires the previously discussed developments in cue-reactivity research.

Furthermore, the clinical application of tDCS targeting relapse prevention in patients with SUD requires optimizing tDCS parameters like montage, duration, and stimulus intensity. Optimal placement of tDCS electrodes must also be considered, as e.g. inhibitory cathodal stimulation of the OFC is a promising alternative to anodal dlPFC stimulation (Chib et al., 2013; Hanlon et al., 2015). We used an electrode placement targeting both stimulus sites to maximize the effect. Therefore, we cannot conclude whether cathode, anode, or both stimulation sites in combination lead to increased connectivity between the OFC and dlPFC. Therefore, the appropriate stimulus site needs to be validated by further empirical evidence.

Unfortunately, the spatial resolution of fNIRS and the size of tDCS electrodes does not allow for the measurement or the stimulation of OFC subdivisions. Nevertheless, there are two distinct subdivisions regarding connectivity and functional meaning within the OFC. While the mOFC encodes subjective stimulus value and reward-guided learning, the lOFC is crucial for reversal learning (extinction), reflecting the modification of reinforcement learning (Fettes et al., 2017). In line with that, successful control of craving was related to decreased mOFC metabolism (Volkow et al., 2010). lOFC activity, however, was discussed as a monitor of behavioral modification related to the most rewarding outcome (Rushworth et al., 2011). To consider these functional dissociations, technical solutions for improvements of spatial assessment need to be developed.

Despite the encouraging results from concurrent fNIRS-tDCS application, there are some technical considerations: OFC and dlPFC activity was only accessible in small parts, as tDCS electrodes are impenetrable to NIR-light. Despite developments in electrode shape, further technical developments, e.g. transparent electrodes allowing the NIR-light to pass, could possibly overcome this restriction.

In addition to the technical concerns, the application context of tDCS also needs to be discussed. In **Study 4**, subjects were instructed to consciously perceive automatized processes elicited by smoking cues, something that is trained during mindfulness practice. Neuroimaging

during mindfulness practice shows increased activity in dmPFC and ACC (Gundel et al., 2018; Grecucci et al. 2015), regions that are highly relevant for SUD. Another finding during mindfulness training was an increased functional connectivity between the dlPFC and the default mode network (superior parietal lobule, middle temporal gyrus; Creswell et al., 2016; Taren et al., 2017). There are common neurobiological mechanisms underlying mindfulness and CET. A pilot study investigating a mindfulness-approach for relapse prevention provided promising results revealing increased ACC and OFC resting state functional connectivity after training (Froelinger et al., 2017). However, if such training effects occur on a biological basis, it will be interesting for further research to capture potential enhancement by neurostimulation. Mindfulness practice is based on increases of cognitive flexibility by the modulation of attentional processes and is therefore highly relevant for relapse prevention in SUD. Mindfulness training restored reward responses to natural and drug cues in the rACC and the ventral striatum (Froelinger et al., 2017). It also reduced stress-related cue-reactivity during smoking cessation (Kober et al., 2017). Therefore, the reduction of stress reactivity may be an underlying mechanism for the efficacy of mindfulness practice in SUD. Amygdala and insula reactivity, closely related to relapse, was likewise reduced by mindfulness training (Kober et al., 2017). Therefore, the impact of stress, clearly an important context factor for relapse, needs to be addressed in further studies. In the current work, the subcortical automatized saliency system was related to dlPFC-mediated cognitive control. Still, our results need to be validated in SUD samples and in different contexts. Likewise, appropriate methods to capture the insula-dependent system (Noel et al., 2013) need to be investigated for a thorough understanding of the context in which modulations of cue-reactivity and cognitive control occur.

### 7.7 General Conclusion

Cue-reactivity was investigated in smokers and heavy social drinkers (HD) without SUD. Cue-reactivity even affected our markers of cognitive control, still we did not find impairments at the behavioral level in HD. Although connectivity effects were highlighted, the underlying compensatory mechanisms could not be fully resolved. In conclusion, a “mindful perspective” in addiction research should be considered, involving context effects. The involvement of context effects in therapeutic interventions and neuroscientific analyses should improve our understanding of cue-reactivity and our interventions for relapse prevention in SUD. This vision requires a solution for some technical issues validated in further research.

**8. Literature**


Anton, R. F., Moak, D. H., & Latham, P. (1995). The Obsessive Compulsive Drinking Scale: a self-rated instrument for the quantification of thoughts about alcohol and drinking behavior. *Alcoholism: Clinical and Experimental Research, 19*(1), 92-99.

Back, S. E., Hartwell, K., DeSantis, S. M., Saladin, M., McRae-Clark, A. L., Price, K. L., ... & Brady, K. T. (2010). Reactivity to laboratory stress provocation predicts relapse to cocaine. *Drug & Alcohol Dependence, 106*(1), 21-27.

Baler, R. D., & Volkow, N. D. (2006). Drug addiction: the neurobiology of disrupted self-control. Trends in molecular medicine, 12(12), 559-566.

Barnes, J. J. M., O'Connell, R. G., Nandam, L. S., Dean, A. J., & Bellgrove, M. A. (2014). Monoaminergic modulation of behavioural and electrophysiological indices of error processing. *Psychopharmacology, 231,* 379-392.

Baumeister, R. F. (2003). Ego depletion and self-regulation failure: a resource model of self-control. *Alcohol Clin Exp Res, 27,* 281-284.

Baumeister, R. F., & Vohs, K. D. (2007). Self-Regulation, ego depletion, and motivation. *Social and personality psychology compass, 1*(1), 115-128.

Bechara, A., & Damasio, H. (2002). Decision-making and addiction (part I): impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. *Neuropsychologia, 40,* 1675-1689.

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). Cognitive therapy of depression. New York: The Guilford Press.

Bell, R. P., Garavan, H., & Foxe, J. J. (2014). Neural correlates of craving and impulsivity in abstinent former cocaine users: Towards biomarkers of relapse risk. *Neuropharmacology, 85,* 461-470.

Berger, H. (1929). Über das Elektrenkephalogramm des Menschen (On the human electroencephalogram). *Archiv f. Psychiatrie u. Nervenkrankheiten, 87,* 527–70.

Berlin, I., Singleton, E.G., & Heishman, S.J. (2013). Predicting smoking relapse with a multidimensional versus a single-item tobacco craving measure. *Drug Alcohol Depend, 132,* 513-520.

Boggio, P. S., Liguori, P., Sultani, N., Rezende, L., Fecteau, S., & Fregni, F. (2009). Cumulative priming effects of cortical stimulation on smoking cue-induced craving. *Neuroscience letters, 463*(1), 82-86.

Boggio, P. S., Sultani, N., Fecteau, S., Merabet, L., Mecca, T., Pascual-Leone, A., Basaglia, A., & Fregni, F. (2008). Prefrontal cortex modulation using transcranial DC stimulation reduces alcohol craving: A double-blind, sham-controlled study. *Drug Alcohol Depend, 92,* 55-60.

Botvinick, M. M. (2007). Conflict monitoring and decision making: reconciling two perspectives on anterior cingulate function. *Cogn Affect Beha. Neurosci, 7,* 356–366.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological review, 108,* 624-652.

Bourque, J., Mendrek, A., Dinh-Williams, L., & Potvin, S. (2013). Neural circuitry of impulsivity in a cigarette craving paradigm. Frontiers in psychiatry, 4.

Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biological psychiatry, 52*(10), 976-986.

Bouton, M.E., & Ricker, S.T. (1994). Renewal of extinguished responding in a second context. *Learning & behavior, 22*(3), 317-324.

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: the Self-Assessment Manikin and the Semantic Differential. *Journal of behavior therapy and experimental psychiatry, 25*, 49-59.

Bradley, M. M., Sabatinelli, D., Lang, P. J., Fitzsimmons, J. R., King, W., & Desai, P. (2003). Activation of the visual cortex in motivated attention. *Behavioral neuroscience, 117*(2), 369.

Brigadoi, S., Ceccherini, L., Cutini, S., Scarpa, F., Scatturin, P., Selb, J., ... & Cooper, R. J. (2014). Motion artifacts in functional near-infrared spectroscopy: a comparison of motion correction techniques applied to real cognitive data. *NeuroImage, 85*, 181-191.

Bunce, S. C., Harris, J. D., Bixler, E. O., Taylor, M., Muelly, E., Deneke, E., Thompson, K. W., & Meyer, R. E. (2015). Possible evidence for re-regulation of HPA axis and brain reward systems over time in treatment in prescription opioid-dependent patients. *Journal of addiction medicine, 9,* 53-60.

Cano, M. E., Class, Q. A., & Polich, J. (2009). Affective valence, stimulus attributes, and P300: color vs. black/white and normal vs. scrambled images. *International journal of psychophysiology : official journal of the International Organization of Psychophysiology, 71*, 17-24.

Carpenter, K. M., Bedi, G., & Vadhan, N. P. (2015). Understanding and Shifting Drug-Related Decisions: Contributions of Automatic Decision-Making Processes. *Current Psychiatry Reports, 17,* 65.

Carpenter, M. J., Saladin, M. E., LaRowe, S. D., McClure, E. A., Simonian, S., Upadhyaya, H. P., & Gray, K. M. (2013). Craving, Cue Reactivity, and Stimulus Control Among Early Stage Young Smokers: Effects of Smoking Intensity and Gender. *Nicotine & Tobacco Research, 17*(4), 463-472.

Carter, B. L., & Tiffany, S. T. (1999). Meta-analysis of cue-reactivity in addiction research. *Addiction, 94,* 327-340.

Carter, C. S., & van Veen, V. (2007). Anterior cingulate cortex and conflict detection: An update of theory and data. *Cognitive, Affective, & Behavioral Neuroscience 7,* 367-379.

Carter, C. S., Macdonald, A. M., Botvinick, M., Ross, L. L., Stenger, V. A., Noll, D., & Cohen, J. D. (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences, 97*(4), 1944-1948.

Cebrian, A. N., Knight, R. T., & Kayser, A. S. (2016). Frontal monitoring and parietal evidence: mechanisms of error correction. *J Cogn Neurosci, 28,* 1166-1177.

Chanraud, S., Martelli, C., Delain, F., Kostogianni, N., Douaud, G., Aubin, H. J., ... & Martinot, J. L. (2007). Brain morphometry and cognitive performance in detoxified alcohol-dependents with preserved psychosocial functioning. *Neuropsychopharmacology, 32*(2), 429.

Chib, V. S., Yun, K., Takahashi, H., & Shimojo, S. (2013). Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Transl. Psychiatry, 3,* e268.

Choi, J., Jung, H. Y., Jin, C., Kang, D., Lee, J., Lee, H., & Park, S. (2011). The Effect of Repeated Virtual Nicotine Cue Exposure Therapy on the Psychophysiological Responses: A Preliminary Study. *Psychiatry investigation, 8,* 155-160.

Clayson, P. E., Clawson, A., & Larson, M. J. (2011). Sex differences in electrophysiological indices of conflict monitoring. *Biological Psychology, 87,* 282-289.

Codispoti, M., Cesarei, A. D., & Ferrari, V. (2012). The influence of color on emotional perception of natural scenes. *Psychophysiology, 49*, 11-16.

Collins, B. N., & Brandon, T. H. (2002). Effects of extinction context and retrieval cues on alcohol cue reactivity among nonalcoholic drinkers. *Journal of consulting and clinical psychology, 70*(2), 390.

Conklin, C. A., & Tiffany, S. T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction, 97,* 155-167.

Conklin, C. A., Perkins, K. A., Robin, N., McClernon, F. J., & Salkeld, R. P. (2010). Bringing the real world into the laboratory: Personal smoking and nonsmoking environments. *Drug and Alcohol Dependence*, *111*(1-2), 58–63.

Conti, C. L., Moscon, J. A., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2014). Cognitive related electrophysiological changes induced by non-invasive cortical electrical stimulation in crack-cocaine addiction. *Int. J. Neuropsychopharmacol., 17*(9), 1465-75.

Courtney, K. E., Schacht, J. P., Hutchison, K., Roche, D. J., & Ray, L. A. (2016). Neural substrates of cue reactivity: association with treatment outcomes and relapse. *Addiction biology, 21*(1), 3-22.

Creswell, J. D., Taren, A. A., Lindsay, E. K., Greco, C. M., Gianaros, P. J., Fairgrieve, A., Marsland, A. L., Brown, K. W., Way, B. M., Rosen, R. J., & Ferris, J. L. (2016). Alterations in Resting-State Functional Connectivity Link Mindfulness Mediation with reduced Interleukin-6: a randomized Controlled trial. *Biol Psychiatry, 80,* 53-61.

Crews, F. T., & Boettiger, C. A., (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology, biochemistry, and behavior, 93,* 237-247.

Cui, X., Bray, S., & Reiss, A. L. (2010). Functional Near Infrared Spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. *Neuroimage, 49*, 3039.

Cutini, S., & Brigadoi, S. (2014). Unleashing the future potential of functional near-infrared spectroscopy in brain sciences. *Journal of Neuroscience Methods, 232,* 152-156.

Cutini, S., Scatturin, P., & Zorzi, M. (2011). A new method based on ICBM152 head surface for probe placement in multichannel fNIRS. *Neuroimage, 54,* 919-927.

da Silva, M. C., Conti, C. L., Klauss, J., Alves, L. G., do Nascimento Cavalcante, H. M., Fregni, F., Nitsche, M. A., & Nakamura-Palacios, E. M. (2013). Behavioral effects of transcranial Direct Current Stimulation (tDCS) induced dorsolateral prefrontal cortex plasticity in alcohol dependence. *J. Physiol. Paris, 107,* 493-502.

Danielmeier, C., & Ullsperger, M. (2011). Post-Error Adjustments. *Front Psychol, 2*, 233.

David, S. P., Munafo, M. R., Johansen-Berg, H., Smith, S. M., Rogers, R. D., Matthews, P. M., & Walton, R. T. (2005). Ventral striatum/nucleus accumbens activation to smoking-related pictorial cues in smokers and nonsmokers: a functional magnetic resonance imaging study. *Biol Psychiatry, 58,* 488-494.

Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D. Y., & Engel, A. K. (2005). Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *J Neurosci, 25,* 11730-11737.

Delgado, M. R., Nearing, K. I., Ledoux, J. E., & Phelps, E. A. (2008). Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. *Neuron 59,* 829-838.

Dempsey, J. P., Harris, K. S., Shumway, S. T., Kimball, T. G., Herrera, J. C., Dsauza, C. M., & Bradshaw, S.D. (2015). Functional near infrared spectroscopy as a potential biological assessment of addiction recovery: preliminary findings. *The American journal of drug and alcohol abuse, 41,* 119-126.

Dhonnchadha, B. Á. N., & Kantak, K. M. (2011). Cognitive enhancers for facilitating drug cue extinction: insights from animal models. *Pharmacology Biochemistry and Behavior, 99*(2), 229-244.

Di Russo, F., & Spinelli, D. (1999). Electrophysiological evidence for an early attentional mechanism in visual processing in humans. *Vision Research, 39*, 2975-2985.

Diana, M. (2011). The dopamine hypothesis of drug addiction and its potential therapeutic value. *Frontiers in psychiatry, 2*.

Dieler, A. C., Dresler, T., Joachim, K., Deckert, J., Herrmann, M. J., & Fallgatter, A. J. (2014). Can intermittent theta burst stimulation as add-on to psychotherapy improve nicotine abstinence? Results from a pilot study. *Eur Addict Res, 20,* 248-253.

Drummond, D. C. (2000). What does cue-reactivity have to offer clinical research? *Addiction, 95 Suppl 2*, 129-144.

Drummond, D. C. (2001). Theories of drug craving, ancient and modern. *Addiction, 96*(1), 33-46.

Du, J., Fan, C., Jiang, H., Sun, H., Li, X., & Zhao, M., (2014). Biofeedback combined with cue-exposure as a treatment for heroin addicts. *Physiol Behav 130*, 34-39.

Duka, T., Trick, L., Nikolaou, K., Gray, M. A., Kempton, M. J., Williams, H., ... & Stephens, D. N. (2011). Unique brain areas associated with abstinence control are damaged in multiply detoxified alcoholics. *Biological psychiatry, 70*(6), 545-552.

Dunning, Parvaz, M. A., Hajcak, G., Maloney, T., Alia-Klein, N., Woicik, P. A., & Goldstein, R. Z. (2011). Motivated Attention to Cocaine and Emotional Cues in Abstinent and Current Cocaine Users: An ERP Study. *The European journal of neuroscience, 33*, 1716-1723.

Dutra, L., Stathopoulou, G., Basden, S. L., Leyro, T. M., Powers, M. B., & Otto, M. W. (2008). A meta-analytic review of psychosocial interventions for substance use disorders. *American Journal of Psychiatry, 165*(2), 179-187.

Edwards, B. G., Calhoun, V. D., & Kiehl, K. A., (2012). Joint ICA of ERP and fMRI during error-monitoring. *Neuroimage, 59,* 1896-1903.

Ehlis, A.-C., Schneider, S., Dresler, T., & Fallgatter, A. J. (2014). Application of functional near-infrared spectroscopy in psychiatry. *Neuroimage, 85,* Part 1, 478-488.

Eichele, T., Debener, S., Calhoun, V. D., Specht, K., Engel, A. K., Hugdahl, K., ... & Ullsperger, M. (2008). Prediction of human errors by maladaptive changes in event-related brain networks. *Proceedings of the National Academy of Sciences, 105*(16), 6173-6178.

Ellis, A. (1962). *Reason and emotion in psychotherapy.* Oxford, England: Lyle Stuart.

Ellis, A. (1973). *Humanistic psychotherapy: The rational-emotive approach.* Three Rivers Press.

Engelmann, J. M., Versace, F., Robinson, J. D., Minnix, J. A., Lam, C. Y., Cui, Y., ... & Cinciripini, P. M. (2012). Neural substrates of smoking cue reactivity: a meta-analysis of fMRI studies. *Neuroimage, 60*(1), 252-262.

Enriquez-Geppert, S., Huster, R. J., & Herrmann, C. S. (2013). Boosting brain functions: Improving executive functions with behavioral training, neurostimulation, and neurofeedback. *International Journal of Psychophysiology, 88*(1), 1-16.

Erblich, J., Bovbjerg, D. H., & Sloan, R. P., (2011). Exposure to Smoking Cues: Cardiovascular and Autonomic Effects. *Addict Behav, 36,* 737-742.

Eriksen, B. A., & Eriksen, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys, 16,* 143-149.

Ernst, L. H., Plichta, M. M., Lutz, E., Zesewitz, A. K., Tupak, S. V., Dresler, T., Ehlis, A.-C., & Fallgatter, A. J. (2013). Prefrontal activation patterns of automatic and regulated approach-avoidance reactions - a functional near-infrared spectroscopy (fNIRS) study. *Cortex, 49,* 131-142.

Evans, J. S. B. T., & Stanovich, K. E. (2013). Dual-Process Theories of Higher Cognition. *Perspectives on Psychological Science*, 8, 223-241.

Everitt, B. J. (2014). Neural and psychological mechanisms underlying compulsive drug seeking habits and drug memories – indications for novel treatments of addiction. *European Journal of Neuroscience, 40,* 2163-2182.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nature neuroscience, 8*(11), 1481-1489.

Falcone, M., Bernardo, L., Ashare, R. L., Hamilton, R., Faseyitan, O., McKee, S. A., Loughead, J., & Lerman, C. (2016). Transcranial Direct Current Brain Stimulation Increases Ability to Resist Smoking. *Brain Stimul., 9,* 191-196.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalogr Clin Neurophysiol, 78,* 447-455.

Feil, J., Sheppard, D., Fitzgerald, P. B., Yücel, M., Lubman, D. I., & Bradshaw, J.L. (2010). Addiction, compulsive drug seeking, and the role of frontostriatal mechanisms in regulating inhibitory control. *Neuroscience & Biobehavioral Reviews, 35*, 248-275.

Ferguson, J., Bauld, L., Chesterman, J., & Judge, K. (2005). The English smoking treatment services: one-year outcomes. *Addiction, 100*(s2), 59-69.

Fettes, P., Schulze, L., & Downar, J. (2017). Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: promising therapeutic targets in psychiatric illness. *Frontiers in systems neuroscience, 11*, 25.

Field, M., & Cox, W. M. (2008). Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and alcohol dependence, 97*, 1-20.

Field, M., Hogarth, L., Bleasdale, D., Wright, P., Fernie, G., & Christiansen, P. (2011). Alcohol expectancy moderates attentional bias for alcohol cues in light drinkers. *Addiction, 106,* 1097-1103.

Field, M., Mogg, K., Zetteler, J., & Bradley, B. P. (2004). Attentional biases for alcohol cues in heavy and light social drinkers: the roles of initial orienting and maintained attention. *Psychopharmacology, 176*, 88-93.

Filbey, F. M., & Dunlop, J. (2014). Differential reward network functional connectivity in cannabis dependent and non-dependent users. *Drug Alcohol Depend, 140,* 101-111.

Folstein, J. R., & Van Petten, C. (2008). Influence of cognitive control and mismatch on the N2 component of the ERP: A review. *Psychophysiology, 45,* 152-170.

Forster, S. E., & Cho, R. Y. (2014). Context Specificity of Post-Error and Post-Conflict Cognitive Control Adjustments. *PLoS ONE*, *9*(3), e90281.

Franken, I. H. A., Dietvorst, R. C., Hesselmans, M., Franzek, E. J., Van De Wetering, B. J. M., & Van Strien, J. W. (2008). CLINICAL STUDY: Cocaine craving is associated with electrophysiological brain responses to cocaine-related stimuli. *Addiction Biology, 13*, 386-392.

Franken, I. H. A., van Strien, J. W., Franzek, E. J., & van de Wetering, B. J. (2007). Error-processing deficits in patients with cocaine dependence. *Biological Psychology, 75*, 45-51.

Franken, I., Luijten, M., van der Veen, F. M., & van Strien, J. W. (2017). Cognitive control in young heavy drinkers: An ERP study. *Drug and Alcohol Dependence, 175,* 77-83.

Fregni, F., Liguori, P., Fecteau, S., Nitsche, M. A., Pascual-Leone, A., & Boggio, P. S. (2008). Cortical stimulation of the prefrontal cortex with transcranial direct current stimulation reduces cue-provoked smoking craving: a randomized, sham-controlled study. *Journal of Clinical Psychiatry, 69*(1), 32-40.

Frese, M., & Keith, N. (2015). Action errors, error management, and learning in Organization. *Annual Review of Psychology*, 66, 661-687.

Froeliger, B., Mathew, A. R., McConnell, P. A., Eichberg, C., Saladin, M. E., Carpenter, M. J., & Garland, E. L. (2017). Restructuring Reward Mechanisms in Nicotine Addiction: A Pilot fMRI Study of Mindfulness-Oriented Recovery Enhancement for Cigarette Smokers. *Evidence-Based Complementary and Alternative Medicine : eCAM*, Vol.*2017*, 7018014.

Fuster, J. M., & Bressler, S. L. (2015). Past Makes Future: Role of pFC in Prediction. Journal of *Cognitive Neuroscience, 27,* 639-654.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin. Neurophysiol., 117,* 845-850.

Garbusow, M., Sebold, M., Beck, A., & Heinz, A., (2014). Too Difficult to Stop: Mechanisms Facilitating Relapse in Alcohol Dependence. *Neuropsychobiology, 70*, 103-110.

Garg, S., Sharma, R., Thapar, S., & Mittal, S. (2016). Visual Evoked Potential Response Among Drug Abusers- A Cross Sectional Study. *Journal of Clinical and Diagnostic Research, 10*, CC23-CC26.

Garland, E., Froeliger, B., & Howard, M. (2014). Neurophysiological evidence for remediation of reward processing deficits in chronic pain and opioid misuse following treatment with Mindfulness-Oriented Recovery Enhancement: exploratory ERP findings from a pilot RCT. *Journal of Behavioral Medicine*, 1-10.

Garland, Eric L., Franken, Ingmar H. A., & Howard, M. O. (2012). Cue-Elicited Heart Rate Variability and Attentional Bias Predict Alcohol Relapse Following Treatment. *Psychopharmacology, 222*, 17-26.

Gehring W. J., & Fencsik D. E. (f2001). Functions of the medial frontal cortex in the processing of conflict and errors. *J Neurosci, 21,* 9430–9437.

Gehring, W. J., & Knight, R. T. (2000). Prefrontal–cingulate interactions in action monitoring. *Nat Neurosci, 3*(5), 516-520.

Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A Neural System for Error Detection and Compensation. *Psychol Sci, 4,* 385-390.

Gehring, W. J., Himle, J., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological science, 11*(1), 1-6.

Glautier, S., & Tiffany, S. T (1995). Methodological issues in cue-reactivity research. In D. C. Drummond, S. T. Tiffany, S. Glautier, & B. Remington (Eds.), *The Wiley series in clinical psychology. Addictive behaviour: Cue exposure theory and practice* (pp. 75-97). Oxford, England: John Wiley.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry, 159*(10), 1642-1652.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature reviews Neuroscience, 12,* 652-669.

Gonzalez-Castillo, J., & Bandettini, P. A. (2017). Task-based dynamic functional connectivity: Recent findings and open questions*. NeuroImage.*

Gorelick, D.A., Zangen, A., & George, M.S., (2014). Transcranial magnetic stimulation in the treatment of substance addiction. *Ann N Y Acad Sci, 1327,* 79-93.

Gray, K. M., LaRowe, S. D., Watson, N. L., & Carpenter, M. J. (2011). Reactivity to in vivo Marijuana Cues Among Cannabis Dependent Adolescents. *Addict Behav, 36,* 140-143.

Grecucci, A., Pappaianni, E., Siugzdaite, R., Theuninck, A., & Job, R. (2015). Mindful emotion regulation: exploring the neurocognitive mechanisms behind mindfulness. *BioMed research international,* 2015.

Gundel, F., von Spee, J., Schneider, S., Haeussinger, F. B., Hautzinger, M., Erb, M., Fallgatter, A. J., & Ehlis, A.-C. (2018). Meditation and the brain – Neuronal correlates of mindfulness as assessed with near-infrared spectroscopy. *Psychiatry Research: Neuroimaging, 271,* 24-33.

Haeussinger F. B., Dresler T., Heinzel S., Schecklmann M., Fallgatter A. J., & Ehlis A. C. (2014). Reconstructing functional near-infrared spectroscopy (fNIRS) signals impaired by extra-cranial confounds: an easy-to-use filter method. *Neuroimage, 95,* 69–79.

Haeussinger, F. B., Heinzel, S., Hahn, T., Schecklmann, M., Ehlis, A.-C., & Fallgatter, A. J. (2011). Simulation of Near-Infrared Light Absorption Considering Individual Head and Prefrontal Cortex Anatomy: Implications for Optical Neuroimaging. *PLoS ONE, 6,* e26377.

Hajcak G., & Nieuwenhuis S. (2006). Reappraisal modulates the electrocortical response to unpleasant pictures. *Cognitive, Affective, & Behavioral Neuroscience, 6*(4), 291–97.

Hajcak, G., Dunning, J. P., & Foti, D. (2009). Motivated and controlled attention to emotion: Time-course of the late positive potential. *Clinical Neurophysiology, 120*, 505-510.

Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing Psychopathology and the Error-Related Negativity. *Psychological Science, 18*(4), 326–333.

Hammersley, R. (1992). Cue exposure and learning theory. *Addictive Behaviors, 17*(3), 297-300.

Hanlon, C. A., Dowdle, L. T., Austelle, C. W., DeVries, W., Mithoefer, O., Badran, B. W., & George, M. S. (2015). What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. *Brain Research, 1628(Pt A)*, 199–209.

Hare T. A., Camerer C. F., & Rangel A. (2009). Self-control in decision-making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648.

Hartmann, A.S., Rief, W., & Hilbert, A. (2011). Psychometric properties of the German version of the Barratt Impulsiveness Scale, Version 11 (BIS-11) for adolescents. *Percept Mot Skills, 112,* 353-368.

Hartwell, K. J., Hanlon, C. A., Li, X., Borckardt J. J., Canterberry, M.; Prisciandaro, J. J., Moran-Santa, M., LeMatty, T., George, M.S., & Brady, K. T. (2016). Individualized real-time fMRI neurofeedback to attenuate craving in nicotine-dependent smokers. *J Psychiatry Neurosci*, 41(1), 48-55.

Hautzinger, M. (1993). Kognitive Verhaltenstherapie und Pharmakotherapie bei Depressionen: Überblick und Vergleich. *Verhaltenstherapie,* 3(1), 26-34.

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences, 110*(11), 4422-4427.

Hayes, S. C. (2016). Acceptance and Commitment Therapy, Relational Frame Theory, and the Third Wave of Behavioral and Cognitive Therapies – Republished Article. Behavior Therapy, 47, 869-885.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict, 86,* 1119-1127.

Heinz, A., Beck, A., Grusser, S. M., Grace, A. A., & Wrase, J. (2009). Identifying the neural circuitry of alcohol craving and relapse vulnerability. *Addict Biol, 14*, 108-118.

Heinzel S., Haeussinger F. B., Hahn T., Ehlis A.-C., Plichta M. M., & Fallgatter A. J. (2013). Variability of (functional) hemodynamics as measured with simultaneous fNIRS and fMRI during inter-temporal choice. *Neuroimage, 71,* 125–134.

Herremans, S. C., & Baeken, C. (2012). The current perspective of neuromodulation techniques in the treatment of alcohol addiction: a systematic review. *Psychiatr Danub, 24*(1), 14-20.

Herrmann M. J., Ehlis A. C., Ellgring H., & Fallgatter A. J. (2005). Early stages (P100) of face perception in humans as measured with event-related potentials (ERPs). *Journal of Neural Transmission, 112*(8), 1073–081.

Herrmann, M. J., Rommler, J., Ehlis, A.-C., Heidrich, A., & Fallgatter, A. J. (2004). Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). *Brain Res Cogn Brain Res, 20,* 294-299.

Herrmann, M. J., Weijers, H. G., Wiesbeck, G. A., Boning, J., & Fallgatter, A. J. (2001). Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. *Alcohol and alcoholism, 36*, 588-593.

Hill, K. E., Samuel, D. B., & Foti, D. (2016). Contextualizing individual differences in error monitoring: Links with impulsivity, negative affect, and conscientiousness. *Psychophysiology, 53*(8), 1143-1153.

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological review, 109,* 679-709.

Huster, R. J., Debener, S., Eichele, T., & Herrmann, C. S. (2012). Methods for simultaneous EEG-fMRI: an introductory review. *J Neurosci, 32,* 6053-6060.

Ide, J. S., Hu, S., Zhang, S., Mujica-Parodi, L. R., & Li, C.-S. R. (2016). Power spectrum scale invariance as a neural marker of cocaine misuse and altered cognitive control. *NeuroImage: Clinical, 11,* 349-356.

Inzlicht, M., Schmeichel, B. J., & Macrae, C. N. (2014). Why self-control seems (but may not be) limited. *Trends in cognitive sciences, 18*(3), 127-133.

Janes, A. C., Pizzagalli, D. A., Richardt, S., Frederick, B. D., Chuzi, S., Pachas, G., Culhane, M. A., Holmes, A. J., Fava, M., Evins, A. E., & Kaufman, M.J. (2010). Brain Reactivity to Smoking Cues Prior to Smoking Cessation Predicts Ability to Maintain Tobacco Abstinence. *Biol Psychiatry, 67,* 722-729.

Jansen, J. M., Daams, J. G., Koeter, M. W. J., Veltman, D. J., van den Brink, W., & Goudriaan, A. E. (2013). Effects of non-invasive neurostimulation on craving: A meta-analysis. *Neuroscience & Biobehavioral Reviews, 37,* 2472-2480.

Jasinska, A. J., Stein, E. A., Kaiser, J., Naumer, M. J., & Yalachkov, Y. (2014). Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. *Neuroscience and biobehavioral reviews, 38*, 1-16.

Jasper, H. (1958). Report of committee on methods of clinical exam in EEG. *Electroencephalogr Clin Neurophysiol, 10*, 370-375.

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology, 146*(4), 373-90.

Jobes, M. L., Aharonovich, E., Epstein, D. H., Phillips, K. A., Reamer, D., Anderson, M., & Preston, K. L. (2015). Effects of Prereactivation Propranolol on Cocaine Craving Elicited by Imagery Script/Cue Sets in Opioid-dependent Polydrug Users: A Randomized Study. *Journal of Addiction Medicine*, *9*(6), 491–498.

Jöbsis, F. F. (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters*. Science, 198*, 1264–1267 .

Jones, K. T, Gözenmann, F., & Berryhill, M. E. (2015). The strategy and motivation influcences on the beneficial effect of neurostimulation: a tDCS and fNIRS stuy. *Neuroimage, 105,* 238-247.

Kabat-Zinn, J. (2003) Mindfulness-based interventions in context: Past, present and future. *Clinical Psychology: Science and Practice, 10,* 144–156.

Kahneman D., Frederick S. (2002). Representativeness revisited: Attribute substitution in intuitive judgment. In Gilovich T., Griffin D., Kahneman D. (Eds*.), Heuristics and biases: The psychology of intuitive judgment (pp. 49–81).* Cambridge, MA: Cambridge University Press.

Kemper, M., Gaschler, R., Schwager, S., & Schubert, T. (2016). The benefit of expecting no conflict—stronger influence of self-generated than cue-induced conflict expectations on Stroop performance. *Acta psychologica, 163,* 135-141.

Karpyak, V. M., Romanowicz, M., Schmidt, J. E., Lewis, K. A. & Bostwick, J. M. (2014). Characteristics of Heart Rate Variability in Alcohol-Dependent Subjects and Nondependent Chronic Alcohol Users. *Alcohol Clin Exp Res, 38*, 9–26.

Kauer, J. (2004). Learning mechanisms in addiction: synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. *Annu Rev Physiol, 66,* 447–475.

Kavanagh, D. J., Statham, D. J., Feeney, G. F., Young, R. M., May, J., Andrade, J., & Connor, J. P. (2013). Measurement of alcohol craving. *Addictive Behaviors, 38*(2), 1572-1584.

Khan, B., Hodics, T., Hervey, N., Kondraske, G. V., Stowe, A. M., & Alexandrakis, G. (2013). Functional near-infrared spectroscopy maps cortical plasticity underlying altered motor performance induced by transcranial direct current stimulation. *Journal of biomedical optics, 18*(11), 116003.

King J. A., Korb F. M., Von Cramon D. Y., & Ullsperger M. (2010). Post-error behavioral adjustments are facilitated by activation and suppression of task-relevant and task-irrelevant information processing. *J Neurosci, 30,* 12759–12769.

Kirilina, E., Jelzow, A., Heine, A., Niessing, M., Wabnitz, H., Bruhl, R., Ittermann, B., Jacobs, A.M., & Tachtsidis, I. (2012). The physiological origin of task-evoked systemic artefacts in functional near infrared spectroscopy. *Neuroimage, 61,* 70-81.

Klauss, J., Penido Pinheiro, L. C., Silva Merlo, B. L., Correia Santos, G. D. A., Fregni, F., Nitsche, M. A., & Miyuki Nakamura-Palacios, E. (2014). A randomized controlled trial of targeted prefrontal cortex modulation with tDCS in patients with alcohol dependence. *International Journal of Neuropsychopharmacology, 17*(11), 1793-1803.

Kober, H., Brewer, J. A., Height, K. L., & Sinha, R. (2017). Neural stress reactivity relates to smoking outcomes and differentiates between mindfulness and cognitive-behavioral treatments. *NeuroImage, 151,* 4-13.

Kober, H., Mende-Siedlecki, P., Kross, E. F., Weber, J., Mischel, W., Hart, C. L., & Ochsner, K. N. (2010). Prefrontal–striatal pathway underlies cognitive regulation of craving. *Proceedings of the National Academy of Sciences, 107,* 14811-14816.

Koob, G. F. (2008). A role for brain stress systems in addiction. Neuron, 59(1), 11-34.

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of Addiction. *Neuropsychopharmacology, 35,* 217-238.

Kopton, I. M., & Kenning, P. (2014). Near-infrared spectroscopy (NIRS) as a new tool for neuroeconomic research. *Frontiers in Human Neuroscience*, *8*, 549.

Körner, A., Geyer, M., & Brähler, E. (2002). Das NEO-Fünf-Faktoren Inventar (NEO-FFI). *Diagnostica, 48,* 19-27.

Kroczek, A. M., Haeussinger, F. B., Fallgatter, A. J., Batra, A., & Ehlis, A.-C. (2017). Prefrontal functional connectivity measured with near-infrared spectroscopy during smoking cue exposure. *Addict Biol, 22(2),* 513-22.

Kroczek, A. M., Haeussinger, F. B., Hudak, J., Vanes, L. D., Fallgatter, A. J., & Ehlis, A.-C. (2018). Cue Reactivity Essentials: Event-Related Potentials During Identification of Visual Alcoholic Stimuli in Social Drinkers. *Journal of Studies on Alcohol and Drugs, 79*(1), 137–147.

Kroczek, A. M., Häußinger, F. B., Rohe, T., Schneider, S., Plewnia, C., Batra, A., Fallgatter, A. J., & Ehlis, A.-C. (2016). Effects of transcranial direct current stimulation on craving, heart-

rate variability and prefrontal hemodynamics during smoking cue exposure. *Drug and Alcohol Dependence*, *168*, 123-127.

Kuhn, S., & Gallinat, J. (2011). Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *Eur J Neurosci 33,* 1318-1326.

Kuo, M. F., Chen, P. S., & Nitsche, M. A. (2017). The application of tDCS for the treatment of psychiatric diseases. *International Review of Psychiatry, 29*, 146–167.

Ladouce, S., Donaldson, D. I., Dudchenko, P. A., & Ietswaart, M. (2017). Understanding Minds in Real-World Environments: Toward a Mobile Cognition Approach. *Frontiers in Human Neuroscience, 10*.

Larson, M. J., & Clayson, P. E. (2011). The relationship between cognitive performance and electrophysiological indices of performance monitoring. *Cogn Affect Behav Neurosci, 11,* 159-171.

Larson, M. J., Clayson, P. E., & Baldwin, S. A. (2012). Performance monitoring following conflict: Internal adjustments in cognitive control? *Neuropsychologia, 50*, 426-433.

Larson, M. J., Clayson, P. E., & Clawson, A. (2014). Making sense of all the conflict: A theoretical review and critique of conflict-related ERPs. *International Journal of Psychophysiology, 93,* 283-297.

Larson, M. J., South, M., & Clayson, P. E. (2011). Sex differences in error-related performance monitoring. *Neuroreport, 22*(1), 44-48.

Lawrence, A. J., Luty, J., Bogdan, N. A., Sahakian, B. J., & Clark, L. (2009). Impulsivity and response inhibition in alcohol dependence and problem gambling. *Psychopharmacology, 207,* 163-172.

LeDoux, J. (2012). Rethinking the Emotional Brain. *Neuron, 73*, 653-676.

Li, Q., Wang, Y., Zhang, Y., Li, W., Yang, W., Zhu, J., Wu, N., Chang, H., Zheng, Y., Qin, W., Zhao, L., Yuan, K., Liu, J., Wang, W., & Tian, J., (2012). Craving correlates with mesolimbic responses to heroin-related cues in short-term abstinence from heroin: an event-related fMRI study. *Brain Res, 1469,* 63-72.

Liao, D. L., Huang, C. Y., Hu, S., Fang, S. C., Wu, C. S., Chen, W. T., Lee, T S. H., Chen, P. C., & Li, C. S. R. (2014). Cognitive Control in Opioid Dependence and Methadone Maintenance Treatment*. PLOS ONE, 9,* e94589.

Lindenmeyer, J. (2005). Behandlung von Alkoholabhängigkeit: “Ich habe kein Verlangen” – Cue reactivity bei Alkoholabhängigen. In P. Neudeck, H.-U. Wittchen, (Hsg.), *Konfrontationstherapie bei psychischen Störungen (S. 201-226).* Göttingen, Deutschland: Hogrefe.

Lindenmeyer, J., & Florin, I. (1998). Testgütekriterien einer deutschen Version des Inventory of Drug Taking Situations für Alkoholabhängige (IDTSA). *Verhaltenstherapie, 8*, 26-36.

Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: A meta-analytic review. *The Behavioral and Brain Sciences*, *35*(3), 121–143.

Linehan M. M. (1993). *Cognitive-Behavioral Treatment of Borderline Personality Disorder.* New York: Guilford.

Littel M., Euser A. S., Munafò, M. R., & Franken I. H. A. (2012). Electrophysiological indices of biased cognitive processing of substance-related cues: a meta-analysis. *Neurosci Biobehav Rev. , 36,* 1803–1816.

Luck, S. J. (2005). *An introduction to the event-related potential technique.* Cambridge, Mass: MIT Press.

Luijten, M., Kleinjan, M., & Franken, I. H. A., (2016). Event-related potentials reflecting smoking cue reactivity and cognitive control as predictors of smoking relapse and resumption. *Psychopharmacology, 233,* 2857-2868.

Luijten, M., Machielsen, M. W. J., Veltman, D. J., Hester, R., de Haan, L., & Franken, I. H. A. (2014). Systematic review of ERP and fMRI studies investigating inhibitory control and error processing in people with substance dependence and behavioural addictions. *J Psychiatry Neurosci, 39,* 149-169.

Luijten, M., O'connor, D. A., Rossiter, S., Franken, I. H., & Hester, R. (2013). Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers. *Addiction, 108*(11), 1969-1978.

Luijten, M., van Meel, C. S., & Franken, I. H. A. (2011). Diminished error processing in smokers during smoking cue exposure. *Pharmacology Biochemistry and Behavior, 97,* 514-520.

Ma, N., Liu, Y., Li, N., Wang, C. X., Zhang, H., Jiang, X. F., … & Zhang, D. R. (2010). Addiction Related Alteration in Resting-state Brain Connectivity. *NeuroImage*, *49*(1), 738–744.

Mainz, V., Drueke, B., Boecker, M., Kessel, R., Gauggel, S., & Forkmann, T. (2012). Influence of cue exposure on inhibitory control and brain activation in patients with alcohol dependence. *Frontiers in Human Neuroscience*, 6 (92).

Mangun, G. R., & Hillyard, S. A. (1991). Modulations of sensory-evoked brain potentials indicate changes in perceptual processing during visual-spatial priming. *Journal of Experimental Psychology: Human Perception and Performance, 17*, 1057-1074.

Mann, K., & Brück, R. (2006). Alkoholismusspezifische Psychotherapie. *Deutscher Ärzteverlag, Köln.*

Mann, K., & Hermann, D. (2010). Individualised treatment in alcohol-dependent patients. Eur Arch Psychiatry Clin Neurosci 260, 116-120.

Mann, K., Loeber, S., Croissant, B., Kiefer, F. (2006). Qualifizierter Entzugsbehandlung von Alkoholabhängigen: Ein Manual zur Pharmako-und Psychotherapie. Deutscher Ärtzeverlag, Köln.

Martin, T., LaRowe, S. D., & Malcolm, R. (2010). Progress in cue exposure therapy for the treatment of addictive disorders: a review update. *The Open Addiction Journal, 3*(1).

Matheus-Roth, C., Schenk, I., Wiltfang, J., Scherbaum, N., & Müller, B. W. (2016). Occipital event-related potentials to addiction-related stimuli in detoxified patients with alcohol dependence, and their association with three-month relapse. *BMC Psychiatry*, *16*, 74.

Matsuda, I., & Nittono, H. (2015). Motivational significance and cognitive effort elicit different late positive potentials. *Clinical Neurophysiology, 126*, 304-313.

McClure, S. M., & Bickel, W. K. (2014). A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training. *Annals of the New York Academy of Sciences, 1327*(1), 62-78.

McKendrick. R., Parasuraman, R., & Ayaz, H. (2015). Wearable functional near infrared spectroscopy and transcranial direct current stimulation (tDCS): expanding vistas for neurocognitive augmentation. *Frontiers in Systems Neuroscience, 9,* 1-14.

McLellan, T., Lewis, D. C., O'Brien, C. P., & Kleber, H. D. (2000). Drug Dependence, a Chronic Medical Illness: Implications for Treatment, Insurance, and Outcomes Evaluation. *JAMA*, 284(13), 1689–1695.

Minnix, J. A., Versace, F., Robinson, J. D., Lam, C. Y., Engelmann, J. M., Cui, Y., & Cinciripini, P. M. (2013). The Late Positive Potential (LPP) in Response to Varying Types of Emotional

and Cigarette Stimuli in Smokers: A Content Comparison. *International journal of psychophysiology, 89*, 18-25.

Mischel, W. (1974). Processes in delay of gratification. *Advances in experimental social psychology, 7,* 249-292.

Molavi, B., & Dumont, G.A. (2012). Wavelet-based motion artifact removal for functional near-infrared spectroscopy. *Physiol Meas, 33,* 259-270.

Monti, P.M., Binkoff, J.A., Abrams, D.B., Zwick, W.R,. Nirenberg, T.D., & Liepman, M.R. (1987) Reactivity of alcoholics and nonalcoholics to drinking cues. *J Abnorm Psychol, 96,* 122–126.

Moran, T. P., Jendrusina, A. A., & Moser, J. S. (2013). The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Research, 1516*, 66-75.

Muraven, M., & Baumeister, R. F. (2000). Self-regulation and depletion of limited resources: Does self-control resemble a muscle? *Psychological Bulletin, 126*(2), 247-259.

Muthalib, M., Kan, B., Nosaka, K., & Perrey, S. (2013). Effects of transcranial direct current stimulation oft he motor cortex on prefrontal cortex activiation during a neuromuscular fatigue task: an fNIRS study, *in Oxygen Transport to Tissue XXXV*, eds S. Van Huffe, G. Naulaers, A. Caicedo, D. F. Bruley. D.K. Harrision (New York: Springer), 73-79.

Myers, K.M., & Carlezon, W.A. (2010). Extinction of drug- and withdrawal-paired cues in animal models: Relevance to the treatment of addiction. *Neuroscience and biobehavioral reviews, 35,* 285-302.

Myers, K. M., & Carlezon, W. A. (2012). D-cycloserine effects on extinction of conditioned responses to drug-related cues. *Biological psychiatry, 71*(11), 947-955.

Naim-Feil, J., & Zangen, A. (2013). *Brain Stimulation: Chapter 49. Addiction* (Vol. 116). Elsevier Inc. Chapters.

Nelson, L. D., Patrick, C. J., Collins, P., Lang, A. R., & Bernat, E. M. (2011). Alcohol impairs brain reactivity to explicit loss feedback. *Psychopharmacology, 218(*2), 419.

Neumann, T., Neuner, B., Gentilello, L. M., Weiss-Gerlach, E., Mentz, H., Rettig, J. S., & Spies, C. D. (2004). Gender differences in the performance of a computerized version of the alcohol use disorders identification test in subcritically injured patients who are admitted to the emergency department. *Alcohol Clin Exp Res, 28*, 1693-1701.

Nguyen-Louie, T. T., Buckman, J. F., Ray, S., & Bates, M. E. (2016). Drinkers' memory bias for alcohol picture cues in explicit and implicit memory tasks. *Drug and Alcohol Dependence*, *160*, 90–96.

Nitsche, M., & Paulus, W. (2007). *Transkranielle Gleichstromstimulation, Das TMS-Buch*, Springer Medizin Verlag, Heidelberg.

Noël, X., Brevers, D., & Bechara, A. (2013). A neurocognitive approach to understanding the neurobiology of addiction. *Current opinion in neurobiology, 23*(4), 632-638.

Norregaard, J., Tonnesen, P., Simonsen, K., Petersen, L., & Säwe, U. (1992). Smoking habits in relapsed subjects from a smoking cessation trial after one year. *Addiction, 87*(8), 1189-1194.

O'Brien, C.P., Childress, A.R., McLellan, T., & Ehrman, R. (1990). Integrating systematic cue exposure with standard treatment in recovering drug dependent patients. *Addict Behav, 15,* 355-365.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97-113.

Olofsson, J. K., Nordin, S., Sequeira, H., & Polich, J. (2008). Affective picture processing: an integrative review of ERP findings. *Biological psychology, 77*, 247-265.

Olvet D.M. & Hajcak G. (2009). The stability of error-related brain activity with increasing trials. *Psychophysiology, 46,* 957-961.

Olvet, D. M., & Hajcak, G. (2008). The error-related negativity (ERN) and psychopathology: toward an endophenotype. *Clinical psychology review, 28*(8), 1343-1354.

Oslin, D. W., Cary, M., Slaymaker, V., Colleran, C., & Blow, F. C. (2009). Daily ratings measures of alcohol craving during an inpatient stay define subtypes of alcohol addiction that predict subsequent risk for resumption of drinking. *Drug and alcohol dependence,* 103(3), 131-136.

Padilla, M. L., Colrain, I. M., Sullivan, E. V., Mayer, B. Z., Turlington, S. R., Hoffman, L. R., Pfefferbaum, A. (2011). Electrophysiological evidence of enhanced performance monitoring in recently abstinent alcoholic men. *Psychopharmacology, 213*(1), 81–91.

Pailing, P. E., & Segalowitz, S. J. (2004). The error-related negativity as a state and trait measure: motivation, personality, and ERPs in response to errors. *Psychophysiology, 41*, 84-95.

Papachristou, H., Nederkoorn, C., Corstjens, J., & Jansen, A. (2012). The role of impulsivity and perceived availability on cue-elicited craving for alcohol in social drinkers. *Psychopharmacology, 224*(1), 145-153. Papachristou, H., Nederkoorn, C., Corstjens, J., & Jansen, A. (2012). The role of impulsivity and perceived availability on cue-elicited craving for alcohol in social drinkers. *Psychopharmacology, 224*(1), 145-153.

Papachristou, H., Nederkoorn, C., Giesen, J. C. A. H., & Jansen, A. (2014). Cue reactivity during treatment, and not impulsivity, predicts an initial lapse after treatment in alcohol use disorders. *Addictive Behaviors, 39*, 737-739.

Pavlov, I. P. (1927). Conditioned reflexes. London: Oxford University Press.

Perry, J. L., & Carroll, M. E. (2008). The role of impulsive behavior in drug abuse. *Psychopharmacology, 200*, 1-26.

Petit, G., Kornreich, C., Maurage, P., Noel, X., Letesson, C., Verbanck, P., & Campanella, S., (2012a). Early attentional modulation by alcohol-related cues in young binge drinkers: an event-related potentials study. *Clin Neurophysiol, 123,* 925-936.

Petit, G., Kornreich, C., Noël, X., Verbanck, P., & Campanella, S. (2012b). Alcohol-Related Context Modulates Performance of Social Drinkers in a Visual Go/No-Go Task: A Preliminary Assessment of Event-Related Potentials. *PLoS ONE, 7*, e37466.

Pfefferbaum, A., Sullivan, E. V., Mathalon, D. H., & Lim, K. O. (1997). Frontal lobe volume loss observed with magnetic resonance imaging in older chronic alcoholics. *Alcoholism: Clinical and Experimental Research, 21*(3), 521-529.

Plewnia, C., Schroeder, P. A., & Wolkenstein, L. (2015). Targeting the biased brain: non-invasive brain stimulation to ameliorate cognitive control. *Lancet Psychiatry, 2,* 351-356.

Plichta, M. M., Heinzel, S., Ehlis, A.-C., Pauli, P., & Fallgatter, A. J. (2007). Model-based analysis of rapid event-related functional near-infrared spectroscopy (NIRS) data: A parametric validation study. *Neuroimage, 35,* 625-634.

Politi, E., Fauci, E., Santoro, A., & Smeraldi, E. (2008). Daily sessions of transcranial magnetic stimulation to the left prefrontal cortex gradually reduce cocaine craving. *American Journal on Addictions, 17*(4), 345-346.

Pulido, C., Mok, A., Brown, S. A., & Tapert, S. F. (2009). Heavy drinking relates to positive valence ratings of alcohol cues. *Addiction biology, 14*(1), 65-72.

Quirk, G. J., Garcia, R., & González-Lima, F. (2006). Prefrontal mechanisms in extinction of conditioned fear. *Biological psychiatry, 60*(4), 337-343.

Rabbitt, P. M. (1966). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology, 71,* 264-272.

Rajan, I., Naga Venkatesha Murthy, P. J., Ramakrishnan, A. G., Gangadhar, B. N., & Janakiramaiah, N. (1998). Heart rate variability as an index of cue reactivity in alcoholics. *Biol Psychiatry, 43,* 544-546.

Rescorla, R. A., & Heth, C. D. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes, 1*(1), 88.

Rissman, J., Gazzaley, A., D'Esposito, M., 2004. Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage, 23,* 752-763.

Rohsenow, D.J., Monti, P. M., & Abrams, D.B. (1995). Methodological issues in cue-reactivity research. In D. C. Drummond, S. T. Tiffany, S. Glautier, & B. Remington (Eds.), *The Wiley series in clinical psychology. Addictive behaviour: Cue exposure theory and practice (pp. 75-97).* Oxford, England: John Wiley.

Rozenkrants, B., Olofsson, J. K., & Polich, J. (2008). Affective visual event-related potentials: arousal, valence, and repetition effects for normal and distorted pictures. *International Journal of Psychophysiology, 67*(2), 114-123.

Rudebeck, P. H., & Murray, E. A. (2014). The orbitofrontal oracle: cortical mechanisms for the prediction and evaluation of specific behavioral outcomes. *Neuron, 84*(6), 1143–1156.

Rushworth, M. F., Noonan, M. P., Boorman, E. D., Walton, M. E., & Behrens, T. E. (2011). Frontal cortex and reward-guided learning and decision-making. *Neuron, 70*(6), 1054-1069.

Sanfey, A. G., & Chang, L. J. (2008). Multiple systems in decision making. *Annals of the New York Academy of Sciences, 1128*(1), 53-62.

Saunders, B., Rodrigo, A. H., & Inzlicht, M. (2016). Mindful awareness of feelings increases neural performance monitoring. *Cognitive, Affective, & Behavioral Neuroscience, 16*(1), 93-105.

Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R., & Grant, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction, 88,* 791-804.

Schacht, J. P., Anton, R. F., & Myrick, H. (2013). Functional neuroimaging studies of alcohol cue reactivity: a quantitative meta-analysis and systematic review. *Addict Biol, 18,* 121-133.

Schellekens, A. F., de Bruijn, E. R., van Lankveld, C. A., Hulstijn, W., Buitelaar, J. K., de Jong, C. A., & Verkes, R. J. (2010). Alcohol dependence and anxiety increase error-related brain activity. *Addiction, 105,* 1928-1934.

Schroder, H. S., Moran, T. P., Moser, J. S., & Altmann, E. M. (2012). When the rules are reversed: Action-monitoring consequences of reversing stimulus–response mappings. Cognitive, Affective, & Behavioral Neuroscience, 12, 629–643.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A Neural Substrate of Prediction and Reward. *Science, 275*, 1593-1599.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T. & Lang, P. J. (2000), Affective picture processing: The late positive potential is modulated by motivational relevance. *Psychophysiology, 37*, 257–261.

Schupp, H. T., Schmälzle, R., Flaisch, T., Weike, A. I., & Hamm, A. O. (2012). Affective picture processing as a function of preceding picture valence: An ERP analysis. Biological psychology, 91(1), 81-87.

Segalowitz, S. J., & Dywan, J. (2009). Individual differences and developmental change in the ERN response: implications for models of ACC function. *Psychological Research PRPF, 73,* 857-870.

Shahbabaie, A., Golesorkhi, M., Zamanian, B., Ebrahimpoor, M., Keshvari, F., Nejati, V., Fregni, F., & Ekhtiari, H. (2014). State dependent effect of transcranial direct current stimulation (tDCS) on methamphetamine craving. *Int J Neuropsychopharmacol, 17*(10), 1591-8.

Shenhav A, Botvinick M. M, Cohen J. D. (2013). The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron,* 79, 217–240.

Shiffman, S., Dunbar, M. S., Kirchner, T. R., Li, X., Tindle, H. A., Anderson, S. J., ... & Ferguson, S. G. (2013). Cue reactivity in non-daily smokers*. Psychopharmacology, 226*(2), 321-333.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. A., & Hickcox, M. (1996). First lapses to smoking: within-subjects analysis of real-time reports. *Journal of consulting and clinical psychology, 64*(2), 366.

Shin, E., Hopfinger, J. B., Lust, S. A., Henry, E. A., & Bartholow, B. D. (2010). Electrophysiological evidence of alcohol-related attentional bias in social drinkers low in alcohol sensitivity. Psychology of addictive behaviors, 24(3), 508.

Silvanto, J., Muggleton, N. G., Cowey, A., & Walsh, V. (2007). Neural adaptation reveals state-dependent effects of transcranial magnetic stimulation. *Eur J Neurosci,* 25, 1874–1881.

Skinner, B. F. (1938). *The Behavior of Organisms: An Experimental Analysis.* Cambridge, Massachusetts: B.F. Skinner Foundation.

Skinner, M. D., Lahmek, P., Pham, H., & Aubin, H.-J. (2014). Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. *PLoS ONE*, *9*(2), e87366.

Smith JL & Mattick RP (2013) Evidence of deficits in behavioural inhibition and performance monitoring in young female heavy drinkers. *Drug Alcohol Depend, 133,* 398-404.

Smith, J. L., Mattick, R. P., & Sufani, C. (2015). Female but not male young heavy drinkers display altered performance monitoring*. Psychiatry Research: Neuroimaging, 233,* 424-435.

Smith, J. L., Mattick, R. P., & Sufani, C. (2017). Error detection and behavioural inhibition in young heavy drinkers. *Drug and Alcohol Dependence, 171,* 20–30.

Sobell, L. C., Agrawal, S., Sobell, M. B., Leo, G. I., Young, L. J., Cunningham, J. A., Simco, E. R., (2003). Comparison of a quick drinking screen with the timeline followback for individuals with alcohol problems. *J Stud Alcohol, 64,* 858-861.

Sofuoglu, M., DeVito, E. E., Waters, A. J., & Carroll, K. M. (2013). Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology, 64*, 452-463.

Sokunbi, M. O., Linden, D. E. J., Habes, I., Johnston, S., & Ihssen, N. (2014). Real-time fMRI brain-computer interface: development of a “motivational feedback” subsystem for the regulation of visual cue reactivity. *Front Behav Neurosci, 8,* 392.

Soshi, T., Ando, K., Noda, T., Nakazawa, K., Tsumura, H., & Okada, T. (2015). Post-error action control is neurobehaviorally modulated under conditions of constant speeded response. *Frontiers in human neuroscience, 8*, 1072.

Stroop, J. R., (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18,* 643-662.

Szegedi, A., Lorch, B., Scheurich, A., Ruppe, A., Hautzinger, M., & Wetzel, H., (2000). Cue exposure in alcohol dependent patients: preliminary evidence for different types of cue reactivity*. J Neural Transm, 107,* 721-730.

Taren, A. A., Gianaros, P. J., Greco, C. M., Lindsay, E. K., Fairgrieve, A., Brown, K. W., ... & Creswell, J. D. (2017). Mindfulness meditation training and executive control network resting state functional connectivity: a randomized controlled trial. *Psychosomatic medicine, 79*(6), 674-683.

Tiffany, S. T (1995). Potential functions of classical conditioning in drug addiction. In D. C. Drummond, S. T. Tiffany, S. Glautier, & B. Remington (Eds.), *The Wiley series in clinical psychology. Addictive behaviour: Cue exposure theory and practice* (pp. 75-97). Oxford, England: John Wiley.

Tiffany S.T., & Conklin C.A. (2000). A cognitive processing model of alcohol craving and compulsive alcohol use. *Addiction, 95,* 145–153.

Townshend, J., & Duka, T. (2001). Attentional bias associated with alcohol cues: differences between heavy and occasional social drinkers. *Psychopharmacology, 157*(1), 67-74.

Unrod, M., Drobes, D. J., Stasiewicz, P. R., Ditre, J. W., Heckman, B., Miller, R. R., ... & Brandon, T. H. (2013). Decline in cue-provoked craving during cue exposure therapy for smoking cessation. *Nicotine & Tobacco Research, 16*(3), 306-315.

van Holst RJ, Schilt T. (2011) Drug-related decrease in neuropsychological functions of abstinent drug users. *Curr Drug Abuse Rev, 4*, 42–56.

Van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology & behavior, 77*(4), 477-482.

Volkow, N. D., Fowler, J. S., & Wang, G.-J. (2003). The addicted human brain: insights from imaging studies. *Journal of Clinical Investigation, 111,* 1444-1451.

*Volkow, N. D., Fowler, J. S., Wang, G. J., Baler, R., & Telang, F. (2009). Imaging dopamine's role in drug abuse and addiction. Neuropharmacology, 56(Suppl 1), 3–8.*

Volkow, N. D., Fowler, J. S., Wang, G. J., Telang, F., Logan, J., Jayne, M., ... & Swanson, J. M. (2010). Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *Neuroimage, 49(3),* 2536-2543.

Vollstädt-Klein, S., Loeber, S., Kirsch, M., Bach, P., Richter, A., Bühler, M., ... & Kiefer, F. (2011). Effects of cue-exposure treatment on neural cue reactivity in alcohol dependence: a randomized trial. *Biological Psychiatry, 69*(11), 1060-1066.

Vollstadt-Klein, S., Loeber, S., Richter, A., Kirsch, M., Bach, P., von der Goltz, C., Hermann, D., Mann, K., & Kiefer, F., (2012). Validating incentive salience with functional magnetic

resonance imaging: association between mesolimbic cue reactivity and attentional bias in alcohol-dependent patients. *Addict Biol, 17,* 807-816.

Walter, M., Dürsteler, K. M., Petitjean, S. A., Wiesbeck, G. A., Euler, S., Sollberger, D. Lang, U. E., & Vogel, M. (2015). Psychosoziale Behandlungen bei Suchterkrankungen-suchstpezifische Psychotherapieformen und ihre Wirksamkeit. *Fortschritte in Neurologie Psychiatrie, 83*(04), 201-210.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology, 54(6), 1063.

*Watson, J. B. (1913). Psychology as the Behaviorist Views it.* Psychological Review*, 20, 158–177.*

Weinberg, A., Kotov, R., & Proudfit, G. H. (2015). Neural indicators of error processing in generalized anxiety disorder, obsessive-compulsive disorder, and major depressive disorder. *Journal of Abnormal Psychology, 124*(1), 172-185.

Wiersema, J. R., van der Meere, J. J., & Roeyers, H. (2007). Developmental changes in error monitoring: an event-related potential study. *Neuropsychologia, 45*(8), 1649-1657.

Wiesner, C. D., & Lindner, C. (2017). Weakening self-control biases the emotional evaluation of appetitive cues. *PLoS ONE*, *12*(1), e0170245.

Wilcox, C. E., Dekonenko, C. J., Mayer, A. R., Bogenschutz, M. P., & Turner, J. A. (2014). Cognitive control in alcohol use disorder: deficits and clinical relevance. *Reviews in the Neurosciences, 25*(1), 1–24.

Wilcox, C.E., Teshiba, T.M., Merideth, F., Ling, J., & Mayer, A.R., (2011). Enhanced Cue Reactivity and Fronto-striatal Functional Connectivity in Cocaine Use Disorders. *Drug Alcohol Depend, 115,* 137-144.

Wiswede, D., Münte, T. F., Krämer, U. M., & Rüsseler, J. (2009). Embodied emotion modulates neural signature of performance monitoring. *PLoS One, 4*(6), e5754.

Wölfling, K., Flor, H., & Grüsser, S. M. (2008). Psychophysiological responses to drug-associated stimuli in chronic heavy cannabis use. *European Journal of Neuroscience, 27*(4), 976-983.

Wrase, J., Grusser, S.M., Klein, S., Diener, C., Hermann, D., Flor, H., Mann, K., Braus, D.F., & Heinz, A., (2002). Development of alcohol-associated cues and cue-induced brain activation in alcoholics. *European psychiatry, 17,* 287-291.

Wundt, W. (1874). *Grundzüge der physiologischen Psychologie.* Leipzig: Engelmann.

Yalachkov, Y., Kaiser, J., & Naumer, M. J. (2012). Functional neuroimaging studies in addiction: Multisensory drug stimuli and neural cue reactivity. *Neuroscience & Biobehavioral Reviews, 36,* 825-835

Yang, Q., Wang, X., Yin, S., Zhao, X., Tan, J., & Chen, A. (2016). Improved emotional conflict control triggered by the processing priority of negative emotion. *Scientific Reports, 6,* 24302.

Yeung, N., & Cohen, J.D. (2006). The Impact of Cognitive Deficits on Conflict Monitoring: Predictable Dissociations Between the Error-Related Negativity and N2. *Psychol Sci, 17,* 164-171.

Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The Neural Basis of Error Detection: Conflict Monitoring and the Error-Related Negativity. *Psychological review, 111,* 931-959.

Yu, J., Tseng, P., Hung, D. L., Wu, S. W., & Juan, C. H. (2015). Brain stimulation improves cognitive control by modulating medial-frontal activity and preSMA-vmPFC functional connectivity. *Human brain mapping, 36*(10), 4004-4015.

Zakiniaeiz, Y., Scheinost, D., Seo, D., Sinha, R., & Constable, R. T. (2017). Cingulate cortex functional connectivity predicts future relapse in alcohol dependent individuals. *NeuroImage: Clinical,* 13, 181-187.

Zama, T., & Shimada, S. (2015). Simultaneous measurement of electroencephalography and near-infrared spectroscopy during voluntary motor preparation. *Scientific Reports*, *5*, 16438.

Zelle, S. L., Gates, K. M., Fiez, J. A., Sayette, M. A., & Wilson, S. J. (2017). The first day is always the hardest: Functional connectivity during cue exposure and the ability to resist smoking in the initial hours of a quit attempt. Neuroimage, 151, 24-32.

Zhang, X., Salmeron, B. J., Ross, T. J., Gu, H., Geng, X., Yang, Y., & Stein, E. A. (2011). Anatomical differences and network characteristics underlying smoking cue reactivity. *Neuroimage, 54,* 131-141.